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Development of Methodologies Employing Rhodium Catalysis and Studies Toward the Total Synthesis of Cortistatin A

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Development of Methodologies Employing Rhodium Catalysis and Studies Toward the Total Synthesis of Cortistatin A

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

December, 2009

Dedication

This dissertation is dedicated to my mother, Suzanne, who was always my number one fan and who raised me to find great joy in learning.

Acknowledgements

First and foremost, I would like to acknowledge my research advisor, Professor Stephen F. Martin, for allowing me the opportunity to study under his tutelage and learn the art of organic synthesis. The intellectually rigorous environment that he provided enabled me to develop my abilities to their fullest extent.

I would like to acknowledge my colleagues Amy Bonaparte, Chris Dockendorff, and Kristen Procko for many helpful and inspiring discussions regarding chemistry, as well as for their humorous camraderie.

I wish to thank Solvias for their generous donation of (*R*)-MeO-BIPHEP ligand, as well as Vince Lynch for his assistance with obtaining crystallographic information.

Finally, I want to thank both the National Science Foundation and Novartis for generous fellowships that supported the majority of my graduate research.

Development of Methodologies Employing Rhodium Catalysis and Studies Toward the Total Synthesis of Cortistatin A

Publication No._____

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The University of Texas at Austin, 2009

Supervisor: Stephen F. Martin

$[Rh(CO)_2Cl]_2$ has been shown to catalyze sequential, mechanistically-distinct transformations in one pot. Tandem allylic alkylation/cycloisomerization sequences have been developed to access valuable, complex structures from relatively simple substrates.

A methodology for the enantioselective conjugate addition of 2-heteroaryl nucleophiles to a variety of Michael acceptors has been developed. This method was used successfully in an ongoing approach to the synthesis of cortistatin A. 10 linear steps have been completed towards the synthesis of cortistatin A, including a highly regioselective propargylation to install a quaternary carbon and a diastereoselective intramolecular Diels-Alder reaction.

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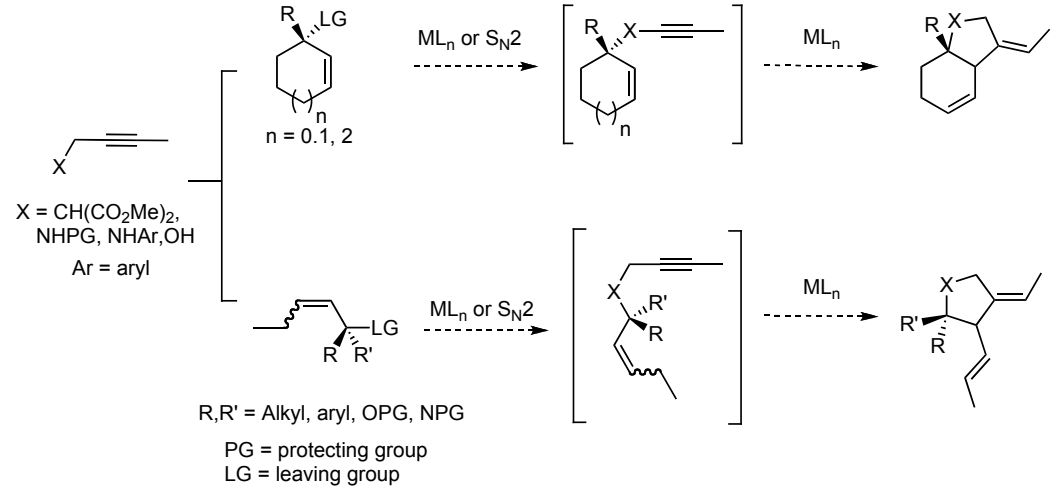
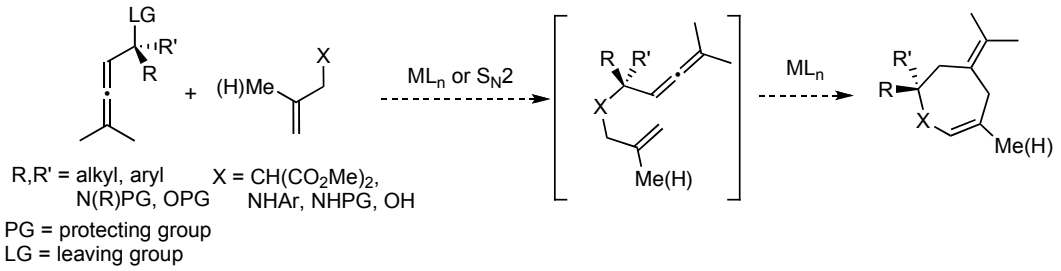
1.1 INTRODUCTION

Vinyl alkylidene cyclopentanes, fused bicyclic 1,4-dienes, and unsaturated medium-sized rings are key structures found within multiple natural products and compounds of biological interest. Consequently, numerous reports have been published on the syntheses of these valuable targets.[1-8] The most commonly employed method to construct these compounds is via transition metal-mediated cycloisomerization of an 1,6-enyne or 1,7-allenene (Schemes 1.1 and 1.2). This synthetic approach requires the synthesis of the intermediate 1,6-enyne or 1,7-allenene, which is often performed via a classical substitution reaction or a transition metal-mediated allylic alkylation.

Scheme 1.1



Scheme 1.2



The synthesis of chiral 1,6-enynes or 1,7-allenenes possessing secondary or tertiary allylic carbons is still a challenging problem because metal-free substitution reactions are typically incompatible with these substrates, and many transition metal-catalyzed allylic alkylation methods suffer from unpredictable or variable regioselectivity, as well as poor stereocontrol, particularly with regard to the stereochemistry at the allylic carbon and the double bond geometry of the starting allylic substrate.[2, 9, 10] Prior research in the Martin group had shown that $[Rh(CO)_2Cl]_2$ is a unique and broadly useful catalyst for promoting allylic alkylations with a wide variety of allylic substrates. Advantages of this catalyst system include a predictable regioselectivity that always furnishes the product resulting from direct substitution of the leaving group, retention of stereochemistry at the allylic carbon, and minimal *E*/*Z* isomerization of double bonds.

We envisioned that our $[Rh(CO)_2Cl]_2$–catalyzed allylic alkylation methodology could not only provide ready access to a variety of challenging 1,6-enyne and 1,7-allenene intermediates, but might also be performed in tandem with the subsequent cycloisomerization as well. Although $[Rh(CO)_2Cl]_2$ was not known to catalyze cycloisomerizations, the transformation has been reported with

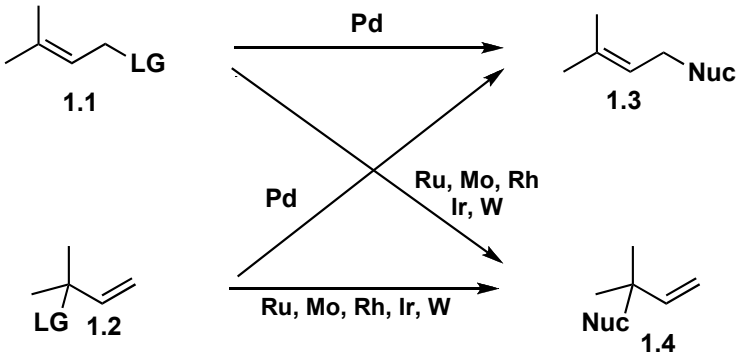
other Rh(I) catalysts and may therefore be viable. Such a domino sequence would be advantageous over current methods to prepare vinyl alkylidene cyclopentanes, fused bicyclic 1,4-dienes, and unsaturated medium-sized rings because it would remove the need to isolate and purify the intermediate enyne or allenene, and would not require the use of two transition metal catalysts. It would allow access to functionally complex carbo- and heterocycles from simple starting materials in a single chemical step. Additionally, the development of methods to catalyze sequential transition metal-mediated transformations in one pot is an extremely challenging and valuable goal and would broaden the current scope of tandem transition metal catalysis.[11]

1.2 UNIQUE ALLYLIC ALKYLATION METHODOLOGY DEVELOPED IN THE MARTIN GROUP

Transition metal-catalyzed allylic alkylations are a widely-utilized and broadly-studied class of reactions for carbon-carbon and carbon-heteroatom bond formations.[2, 9, 10] A variety of metals, including Pd, Mo, Ir, Rh, Ru, and W, have been reported to catalyze allylic alkylations.

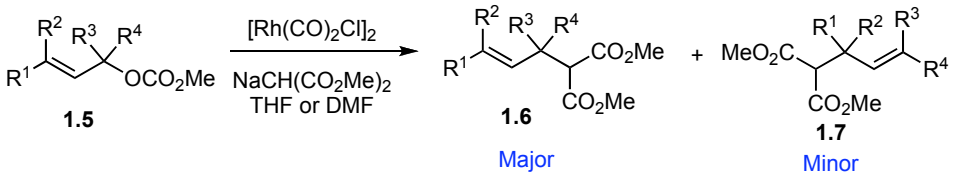
Typically, the regioselectivity of transition metal-catalyzed allylic alkylations arise from a metal-specific bias for either the less or more substituted terminus of the allylic substrate (Scheme 1.3). Ruthenium, molybdenum, rhodium, iridium, and tungsten typically favor substitution at the more hindered allylic terminus, whereas palladium often exhibits the opposite bias.[2, 12] Although this is an established trend, it should be noted that these biases can be overcome in some cases via ligand manipulation.[13]

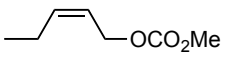
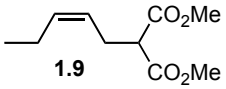
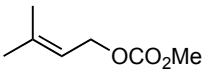
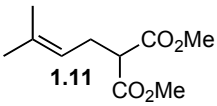
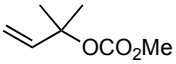
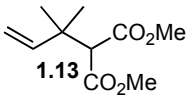
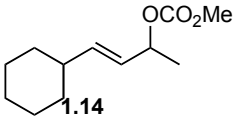
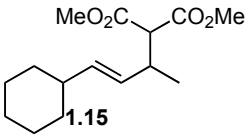
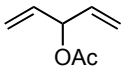
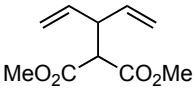
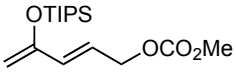
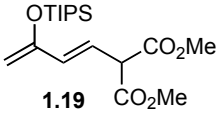
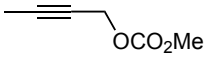
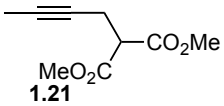
Scheme 1.3



Previous investigations in the Martin group had revealed that the commercially available complex $[Rh(CO)_2Cl]_2$ catalyzes allylic alkylations with a unique regioselectivity distinct from the trends typically observed.[14] Generally, $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations proceed with direct substitution of the leaving group, *irrespective of the substitution at the allylic termini*.[14] These advantageous properties were utilized by the Martin group in a variety of $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations with a diverse array of substrates, thereby establishing $[Rh(CO)_2Cl]_2$ as a unique and broadly useful catalyst for promoting allylic alkylations (Table 1.1).

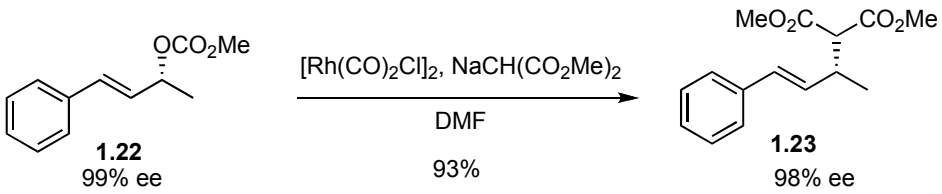
Table 1.1



Entry	Allylic Carbonate	Alkylation Product	Yield	Ratio (Major :Minor)
1	 **1.8**	 **1.9**	86	99:1 (97:3 *cis*:*trans*)
2	 **1.10**	 **1.11**	75	92:8
3	 **1.12**	 **1.13**	80	94:6
4	 **1.14**	 **1.15**	94	93:7
5	 **1.16**	 **1.17**	74	96:4
6	 **1.18**	 **1.19**	80	94:6
7	 **1.20**	 **1.21**	52	99:1

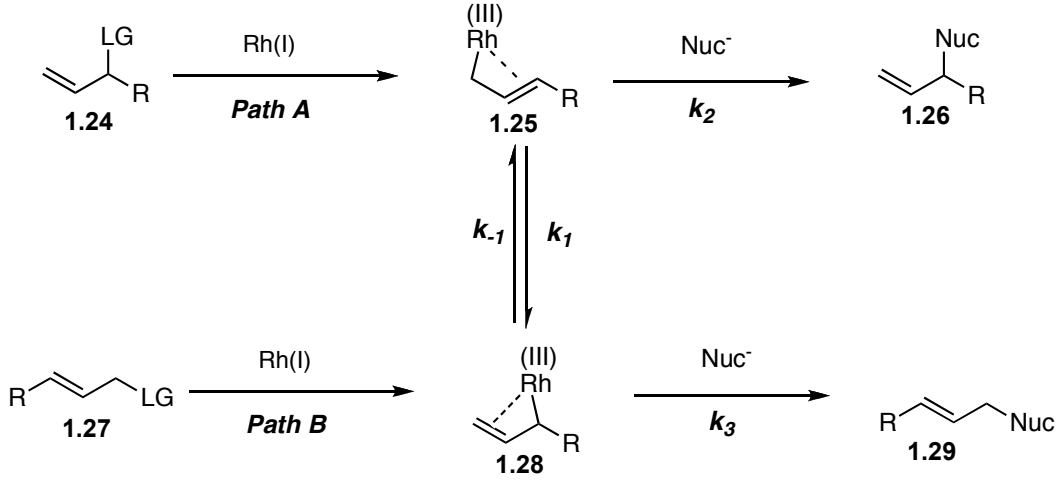
Additionally, $[Rh(CO)_2Cl]_2$-catalyzed allylations proceed with preservation of the *E*/*Z* stereochemistry (Table 1.1, entry 1) and enantiopurity of the starting allylic substrate (Scheme 1.4).[14]

Scheme 1.4



The mechanistic explanation for this unique regioselectivity has not yet been determined. However, some insights may be found in the work of Andrew Evans who has observed similar regioselectivity in a very limited number of cases, using a catalyst derived from $Rh(PPh_3)Cl$ and phosphite ligands.[15] He proposed that a σ+π "enyl" complex **1.25** or **1.28** is formed, that in the presence of a nucleophile undergoes substitution faster than σ-π-σ isomerization (Scheme 1.5).

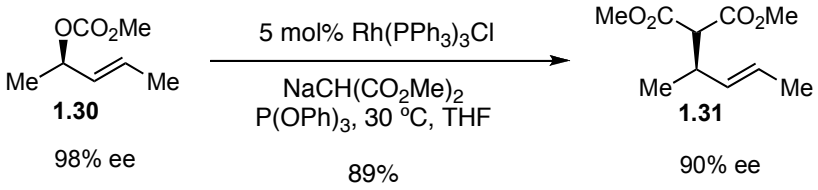
Scheme 1.5



Additionally, Evans found that enantiomeric excess was largely maintained in enantiomerically enriched allylic carbonates (Scheme 1.6). This result provided additional evidence that the reaction proceeds via an enyl

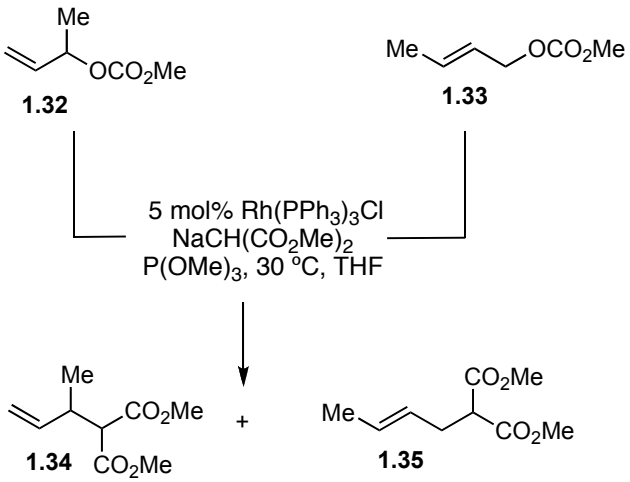
complex, as the corresponding σ species would have undergone rapid bond rotation, leading to erosion of the enantiomeric excess. According to Evans's rationale, our similar observation that $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations proceed with retention of enantiomeric excess suggests that our catalytic cycle is proceeding via an enyl complex (Scheme 1.4).

Scheme 1.6



Although Evans's observations are similar to our work, it is important to note that they were only seen in very specific cases, namely those in which steric biases did not overwhelm this "memory effect." For example, when Evans submitted differentially substituted allylic carbonates **1.32** and **1.33** to the same reaction conditions, only **1.32** led to excellent selectivity in favor of the product arising from direct substitution of the leaving group (Scheme 1.7). In the case of **1.33**, the opposite regioselectivity was favored, indicating that substitution at the allylic termini can override the memory effect. This is contrasted by our work (Table 1.1, entries 2 and 3) in which differentially substituted allylic carbonates furnish products arising from direct substitution of the product, thus emphasizing the extensive nature of the memory effect in our method.

Scheme 1.7



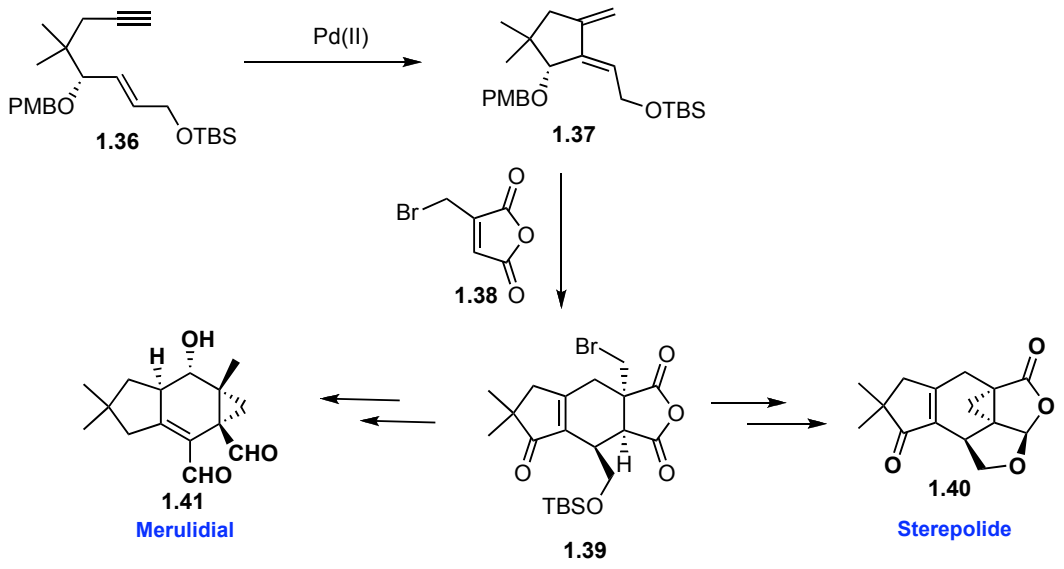
From **1.32** = 42:1, 99%
From **1.33** = 2:1, 83%

1.3 1,6-ENYNE CYCLOISOMERIZATIONS

Enyne cycloisomerizations have also proven to be an extremely useful class of reactions, having been employed as key steps in a variety of natural product syntheses.[6] The cyclization of enynes to 1,4-dienes in the absence of transition metal catalysts, also known as the intramolecular Alder-ene reaction, tends to be either extremely difficult or impossible, depending upon the substrate. In those cases where it can be performed, temperatures in excess of 400 ˚C are commonly necessitated. The discovery that transition metals can catalyze this transformation at much lower temperatures has greatly broadened the scope and practicality of this reaction, resulting in its wide-spread use. To date, a variety of metals have been used to catalyze the cycloisomerization of enynes, including palladium, rhodium, ruthenium, platinum, iridium, gold, and nickel-chromium complexes.[7, 16-18]

Of the variety of metals that catalyze enyne cycloisomerizations, palladium catalysis has been employed most frequently, with Trost contributing the bulk of the research in this area. One report involves the cycloisomerization of **1.36** in the presence of a Pd(II) catalyst to yield **1.37** in 91% yield. This intermediate was elaborated into two natural products, sterepolide and merulidial (Scheme 1.8).[4] Although both 1,3- and 1,4-dienes can be formed via Pd-catalysis, Trost observed that oxygen substitution at the allylic position facilitates the exclusive formation of 1,3-dienes, a characteristic that was exploited in the sterepolide and merulidial syntheses.

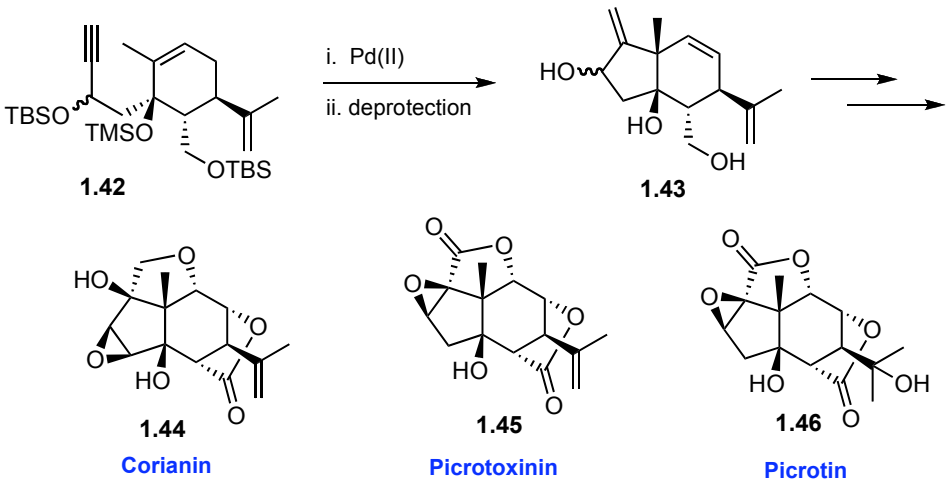
Scheme 1.8



Trost has also demonstrated that cyclic alkenes could be used in intramolecular 1,6-enyne Pd-catalyzed cycloisomerizations, enabling access to bicyclic intermediates. This reaction was highlighted in his syntheses of corianin, picrotoxinin, and pictrotin (Scheme 1.9).[3, 6] In these examples, a 1,4-diene was

produced exclusively due to lack of a β-hydrogen atom that would allow access to the 1,3-diene.

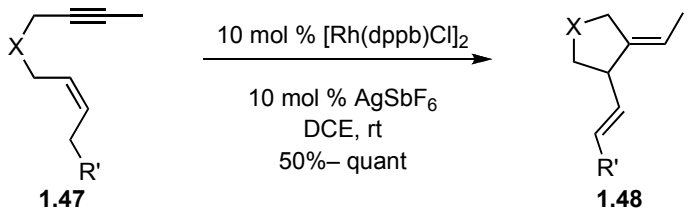
Scheme 1.9



1.3.1 Rh(I)-Catalyzed 1,6-Enyne Cycloisomerizations

Although 1,6-enyne cycloisomerizations catalyzed by $[Rh(CO)_2Cl]_2$ have not been explicitly reported, products arising from such reactions have been isolated in minor amounts in Pauson-Khand reactions catalyzed by $[Rh(CO)_2Cl]_2$.[19] In the broader area of Rh(I) catalysis, Zhang and coworkers have reported the cycloisomerization of 1,6-enynes with the cationic catalyst $[Rh(dppb)]^+$, which was derived from $[Rh(dppb)Cl]_2$ and $AgSbF_6$ (Scheme 1.10).[20] Zhang successfully used this method to access heterocycles, as well as carbocycles.

Scheme 1.10

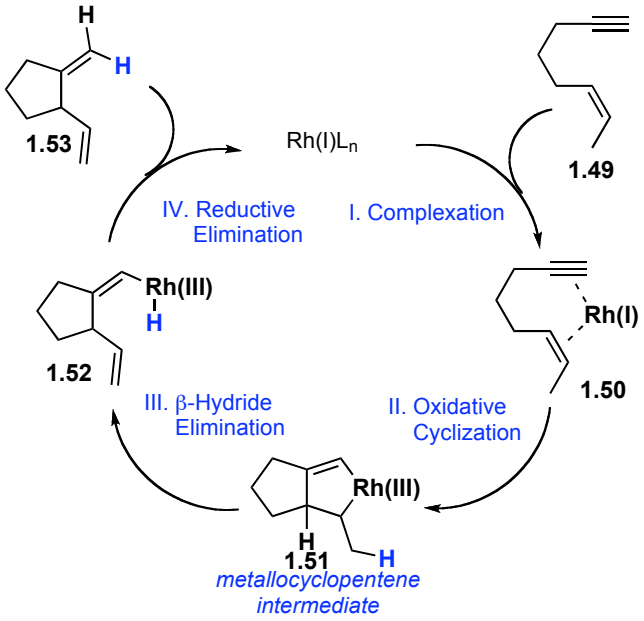


1.47 **1.48**

X = $C(CO_2Et)_2$, O, NSO_2Ph

Zhang proposed a catalytic cycle similar to that reported by Trost.[7] The first step is complexation of rhodium to both the alkene and alkyne moieties to form **1.50**. Oxidative cyclization affords a metallocyclopentene intermediate **1.51**, which undergoes β-hydride elimination to form either a 1,3- or 1,4-diene, although Zhang observed only the 1,4-diene product. Reductive elimination of **1.52** furnishes the product **1.53** and regenerates the active catalyst. Zhang reported that a cationic catalyst is crucial because a highly coordinatively unsaturated environment is necessary for the formation of the metallacyclopentene intermediate **1.51** (Figure 1.1).

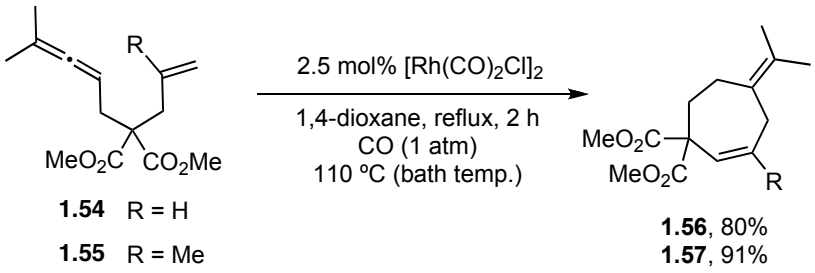
Figure 1.1



1.4 1,7-ALLENENE CYCLOISOMERIZATIONS

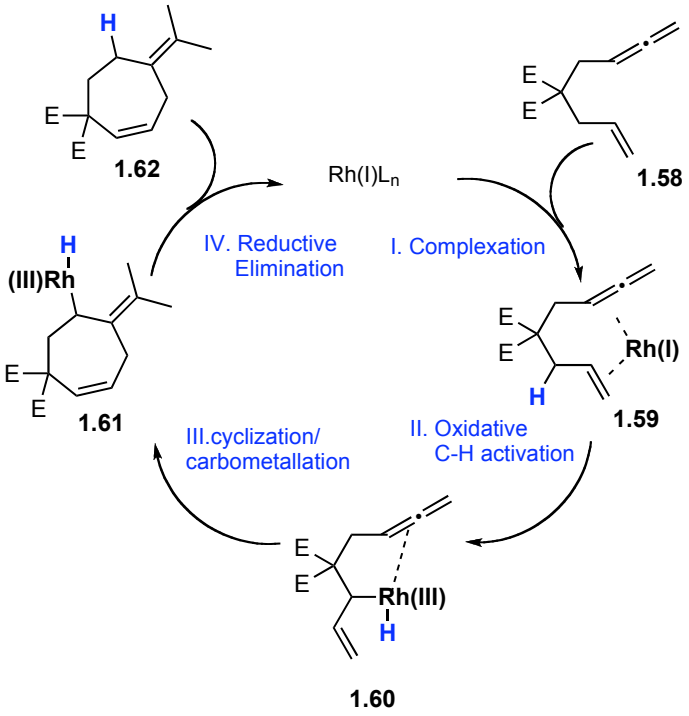
Itoh and coworkers have shown that 1,7-allenenes **1.54** and **1.55** undergo $[Rh(CO)_2Cl]_2$-catalyzed cycloisomerizations to produce unsaturated medium-sized rings **1.56** and **1.57** (Scheme 1.11).[8] Itoh found that use of a CO atmosphere led to small increases in yield.

Scheme 1.11



Although the mechanism of this reaction is unknown, Itoh proposed a possible catalytic cycle (Figure 1.2). Itoh postulated that initial complexation of rhodium to the terminal alkene and inner double bond of the allene affords **1.59**. Allylic C-H activation furnishes **1.60**, which undergoes cyclization and carbometallation to provide **1.61**. Finally, a reductive elimination occurs to yield the observed product **1.62**. Itoh did not remark on the selectivity of the reductive elimination, but it may be driven by the formation of the more highly substituted double bond.

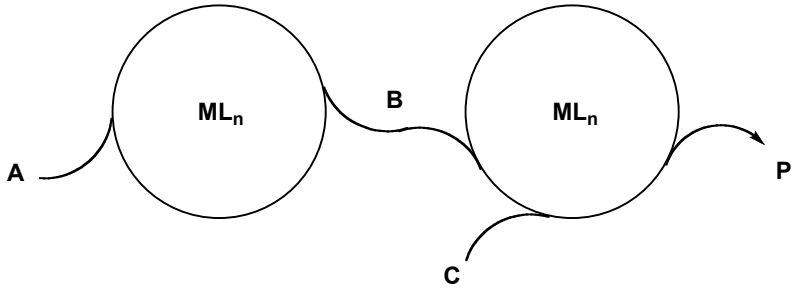
Figure 1.2



1.5 TANDEM CATALYSIS

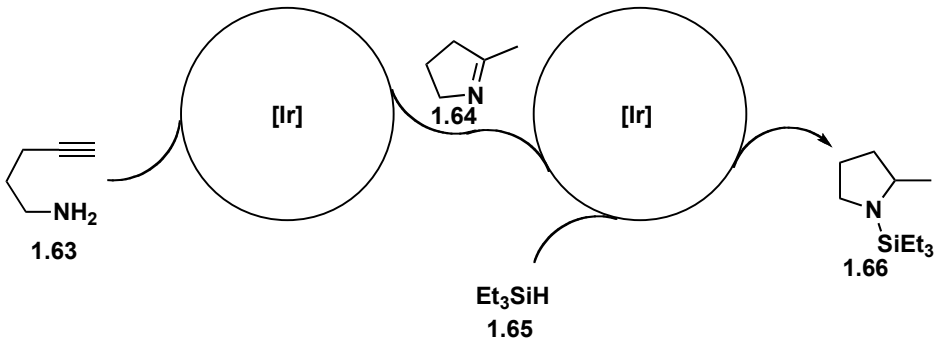
Tandem catalysis has been defined by Bazan and coworkers as "synthetic strategies that involve the sequential use of catalytic reactions with minimal change in conditions."[21] The product of the first catalytic cycle becomes the reactant for the second catalytic cycle (Scheme 1.12) and can involve single or multiple catalysts.

Scheme 1.12



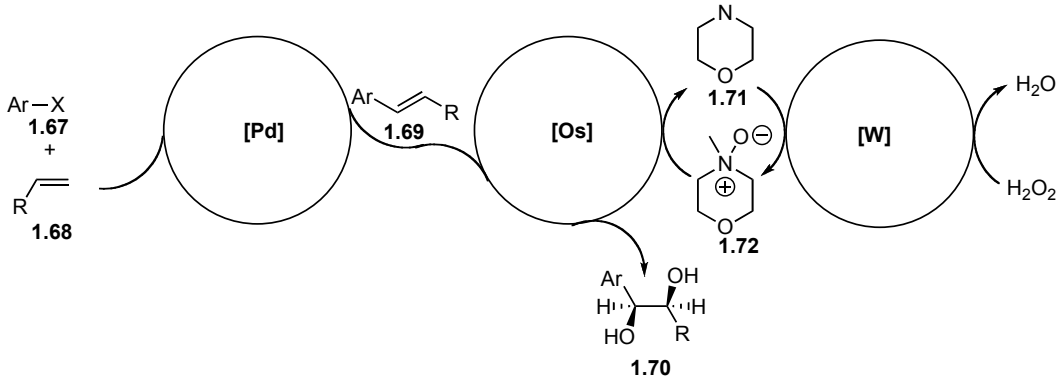
An example of tandem catalysis employing a single catalyst has been reported by Wren and coworkers, [22] in which an Ir-catalyzed hydroamination furnished an imine intermediate **1.64**, which then participated in an Ir-catalyzed hydrosilation to generate **1.66** in good yield (Scheme 1.13).

Scheme 1.13



Choudary has reported an example of tandem catalysis employing multiple catalysts embedded in a layered double-hydroxide (LDH) matrix. Using Na_2PdCl_4, K_2OsO_4, and Na_2WO_4, Choudary created a trifunctional LDH-embedded catalyst that facilitated a Heck coupling, asymmetric dihydroxylation, and oxidation of *N*-methylmorpholine to *N*-methylmorpholine *N*-oxide (Scheme 1.14). This sequence produced 1,2-diols in good yield and with excellent enantiomeric excess.

Scheme 1.14

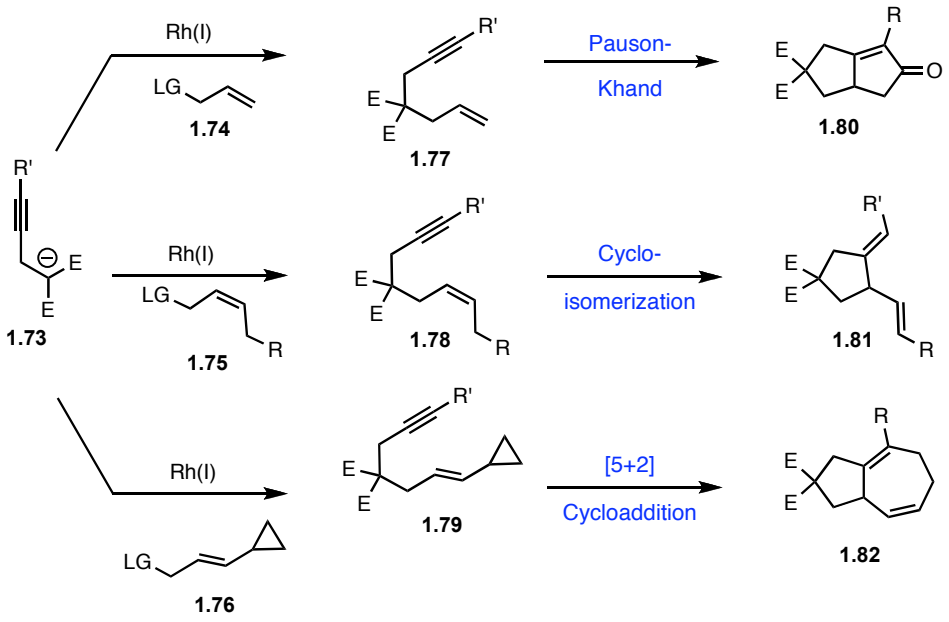


The advantages to using tandem catalysis are numerous. Product yields can be greatly increased due to the avoidance of the isolation and purification of intermediates. In those cases when such intermediates are dangerous and highly reactive, this advantage results in increased personal and environmental safety. In addition, limitations presented by equilibrium-limited reactions can be overcome if they are performed in tandem with subsequent reactive catalytic cycles. In those cases, rapid consumption of the intermediate facilitates a constant funnelling of starting material into product in the equilibrium-limited process.

1.6 COMBINING ALLYLIC ALKYLATIONS WITH OTHER PROCESSES

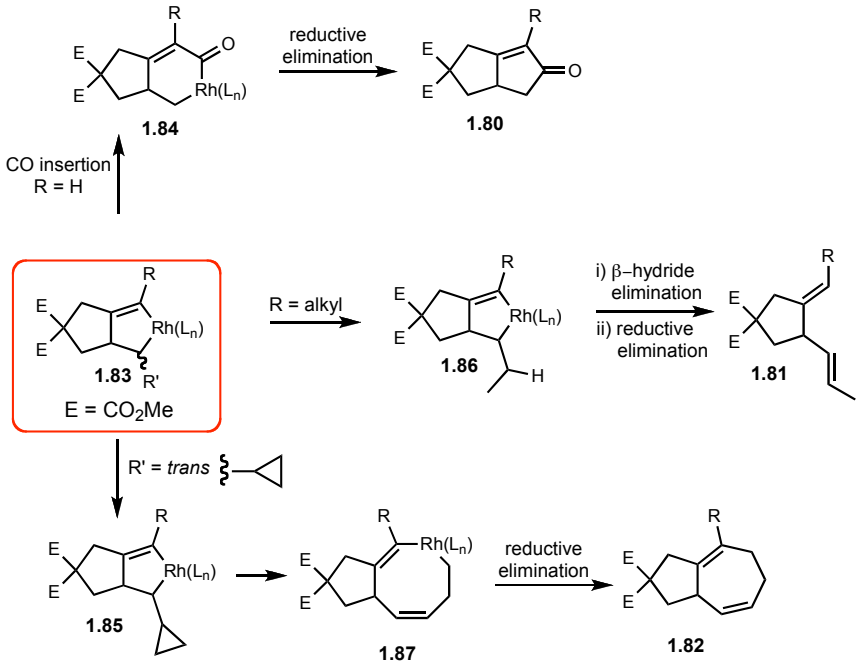
By combining our allylic alkylation methodology with other rhodium(I)-catalyzed transformations, we envisioned that $[Rh(CO)_2Cl]_2$ might be used to catalyze mechanistically distinct transformations in novel domino reaction sequences. Since propargyl malonates had been shown to be compatible nucleophiles in the allylic alkylation step, we could easily access intermediate 1,6-enynes, which are known to undergo Rh(I)-catalyzed carbocyclizations, including Pauson-Khand reactions,[23, 24] enyne cycloisomerizations,[25] and [5+2] cycloadditions.[26, 27] We envisioned three tandem sequences involving an initial allylic alkylation with a propargyl malonate, followed by one of several carbocyclizations (Scheme 1.15).

Scheme 1.15



The three proposed tandem sequences share mechanistic similarities, insomuch as they have all been proposed to proceed via a metallocyclopentene intermediate (Figure 1.3). From this common intermediate, divergent pathways are available depending upon the nature of the R' group and the reaction conditions. If R' is a cyclopropyl group, then a [5+2] cycloaddition will commence. If R' is an alkyl group or hydrogen, the reaction conditions will determine the ensuing pathway. Namely, under a CO atmosphere a Pauson-Khand reaction will occur, whereas in the absence of a CO atmosphere, an enyne cycloisomerization will be favored.

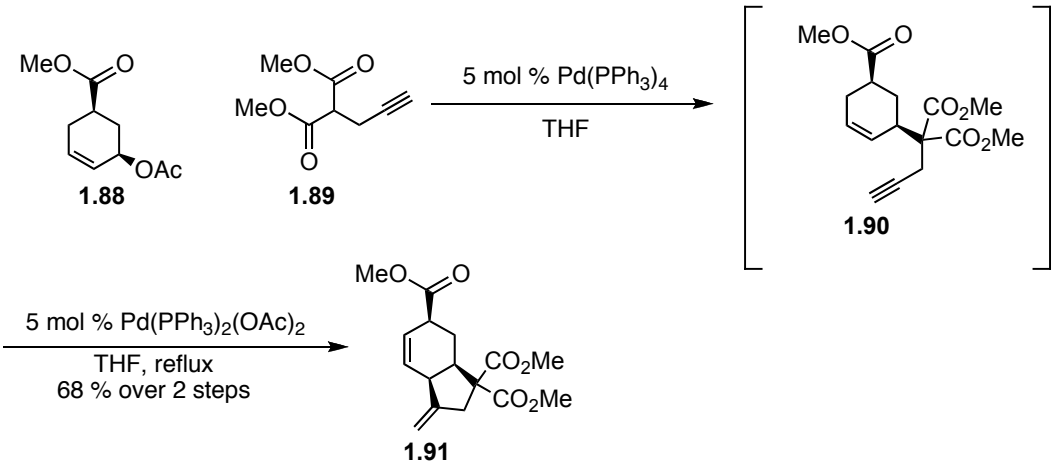
Figure 1.3



A tandem allylic alkylation/[5+2] cycloaddition has not been reported previously, and only one example of a tandem allylic alkylation/1,6-enyne

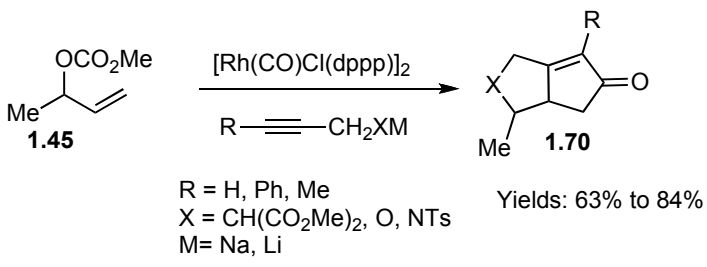
cycloisomerization has been reported by Trost. However, the chemistry reported by Trost suffers from the need to employ multiple catalysts (Scheme 1.16). Our strategy, on the other hand, seeks to use a single catalyst to perform mechanistically distinct transformations, which would offer much greater atom economy and efficiency than Trost's method.

Scheme 1.16



Evans reported a tandem Rh-catalyzed allylic alkylation/Pauson-Khand with the use of $[RhCl(CO)dppp]_2$ (Scheme 1.17).[28] The use of our methodology in such a sequence would offer increased practicality with the use of ligand-free reaction conditions and commerically available catalyst.

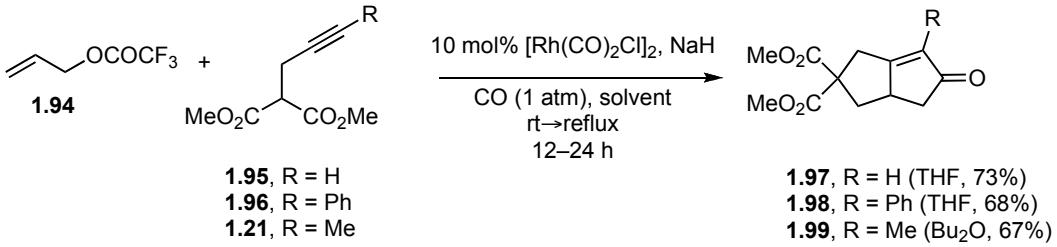
Scheme 1.17



1.7 ALLYLIC ALKYLATION/PAUSON-KHAND SEQUENCE

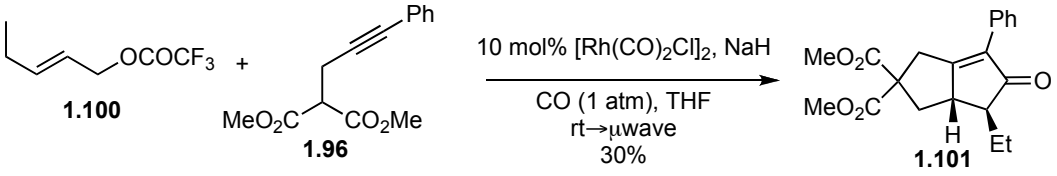
The $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/Pauson-Khand tandem sequence was developed by Kenny Miller. Several propargyl malonates added successfully to allylic trifluoroacetate **1.94** and subsequent heating under a carbon monoxide atmosphere furnished the Pauson-Khand adducts in 67% to 73% yields (Scheme 1.18).[29]

Scheme 1.18



When substituted allylic trifluoroacetates were used, low yields of Pauson-Khand adducts could be obtained with microwave heating (Scheme 1.19). This result is important as the allylic alkylation of **1.100** with Evans's conditions would either lead to the undesired regioisomer or a mixture of regioisomers.

Scheme 1.19

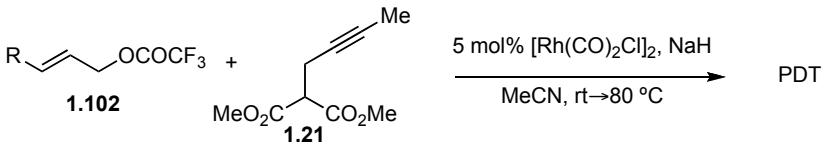


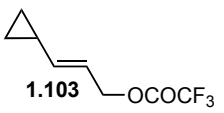
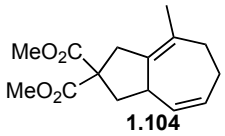
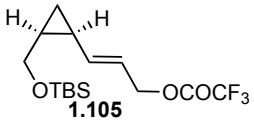
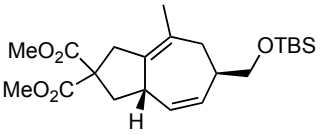
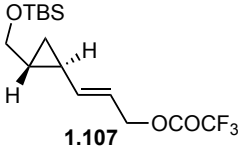
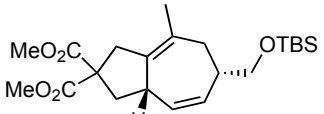
1.8 ALLYLIC ALKYLATION/[5+2] CYCLOADDITION SEQUENCE

The $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/Pauson-Khand tandem sequence was developed by Brandon Ashfeld. Excellent yields were obtained for

the sequence with both racemic and chiral allylic substrates (Table 1.2).[29] Regio- and diasteroselectivities observed were consistent with prior work reported by Wender (Table 1.2, entries 2 and 3).[30]

Table 1.2



Entry	Allylic Substrate	PDT	Yield(%)	Regioslectivity
1	 **1.103**	 **1.104**	89	n/a
2	 **1.105**	 **1.106**	83	1:0
3	 **1.107**	 **1.108**	92	9:1

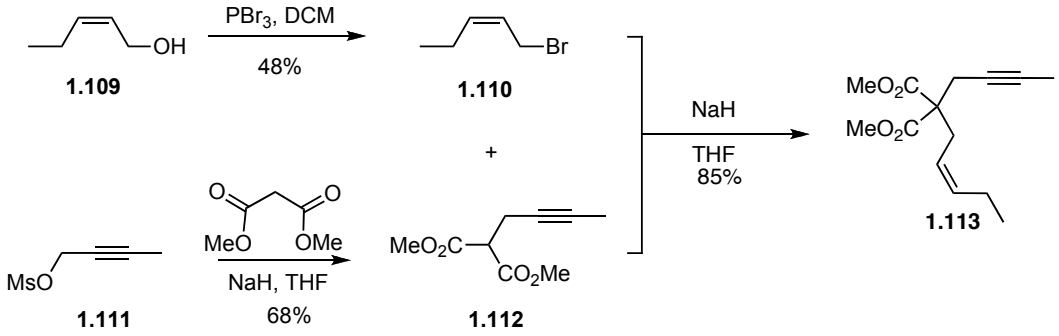
n/a = not applicable

1.9 DEVELOPMENT OF $[Rh(CO)_2Cl]_2$-CATALYZED TANDEM ALLYLIC ALKYLATION/CYCLOISOMERIZATION SEQUENCES

As the cycloisomerization of 1,6-enynes with a neutral Rh(I) species, such as $[Rh(CO)_2Cl]_2$, is unprecedented, our initial studies of a tandem allylic alkylation/cycloisomerization sequence began by establishing the efficacy of this single transformation. Enyne **1.113** was prepared from the reaction of malonate

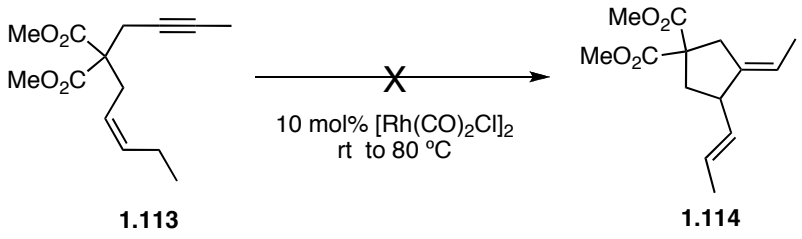
1.112 with allylic bromide **1.110** in the presence of sodium hydride. Malonate **1.112** was prepared from the corresponding mesylate **1.111**, and **1.110** was synthesized by bromination of the corresponding alcohol **1.109**. (Scheme 1.20).

Scheme 1.20



Because Zhang had reported that cycloisomerizations of enynes can proceed at room temperature with cationic Rh(I) catalysts, the cycloisomerization of **1.113** was first attempted at room temperature in a variety of solvents with 10 mol% of $[Rh(CO)_2Cl]_2$ (Scheme 1.21). This reaction failed to yield product, and only starting material was recovered. The temperature of the reaction was steadily increased, but even at 80˚C, only starting material was recovered.

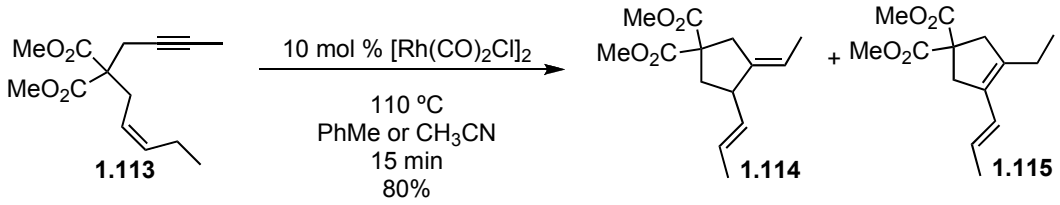
Scheme 1.21



Solvents Screened: DMF, THF, PhMe, CH_3CN, DCE

More forcing conditions were employed until finally we found that when **1.113** was heated in toluene or acetonitrile at 110 ˚C in a sealed vial, efficient conversion to the cycloisomerization product **1.114** was observed (Scheme 1.22). A minor amount (4%) of the conjugated diene **1.115** was also observed. This result represents the first 1,6-enyne cycloisomerization catalyzed by a neutral Rh(I) species.

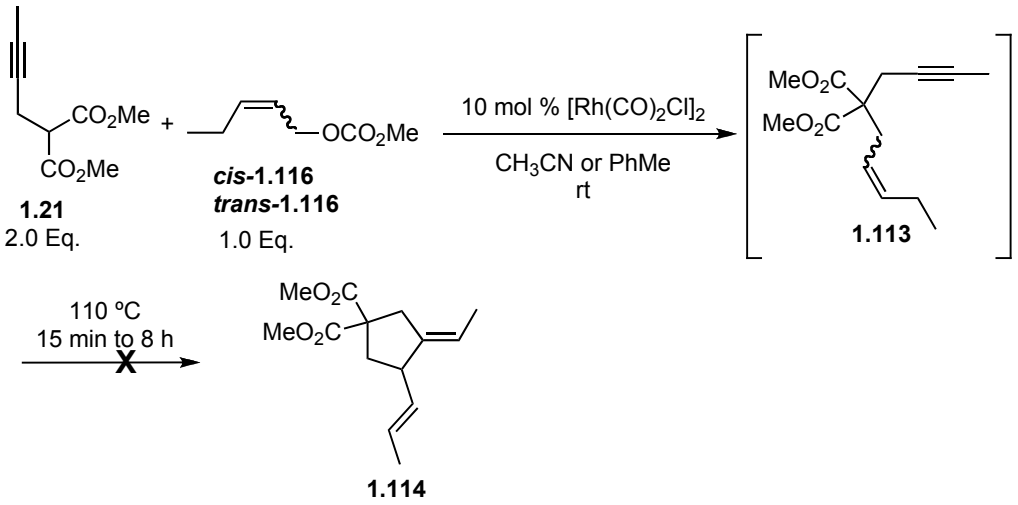
Scheme 1.22



1.9.1 Combining the Allylic Alkylation and Enyne Cycloisomerization

We next focused on performing both the allylic alkylation and cycloisomerization in one pot. Allylic carbonates *cis*- and *trans*-**1.116** were both employed in order to probe the effect of *E*/*Z* stereochemistry upon the cycloisomerization. Despite prolonged reaction times, the domino sequence with both of these carbonates were unsuccessful, and only the intermediate enyne **1.113** was recovered (Scheme 1.23).

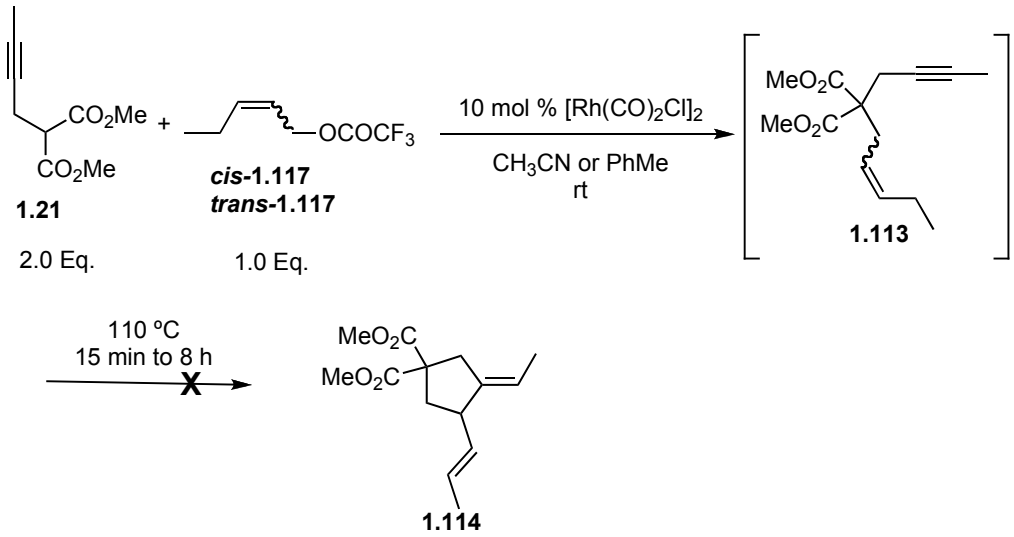
Scheme 1.23



This result was not entirely unexpected as both Kenny Miller and Brandon Ashfeld had found that the allylic alkylation/Pauson Khand and allylic alkylation/[5 + 2] cycloaddition domino sequences necessitated the use of an allylic trifluoroacetate to proceed with high efficiency. The use of allylic carbonates in those domino sequences failed to yield the desired products. Although the reason for this incompatibility of allylic carbonates with tandem catalysis is not entirely understood, it was postulated that the carbonate released in the allylic alkylation step might act as a ligand, thereby altering the metal species such that it no longer catalyzes the subsequent carbocyclization.

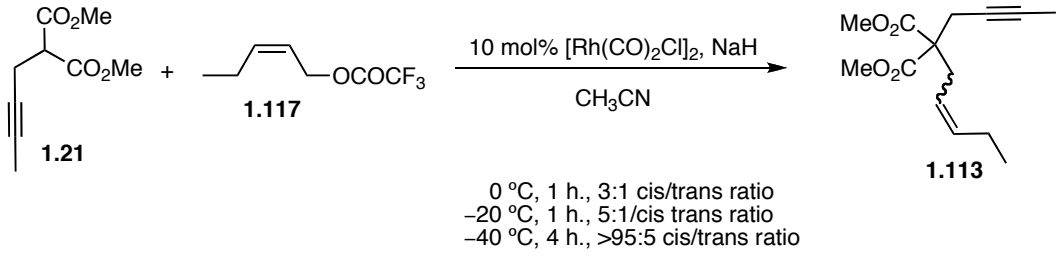
In light of these findings, the domino sequence was next attempted with the allylic trifluoroacetates *cis*- and *trans*-**1.117**, which were prepared from the corresponding alcohols immediately prior to use. Unfortunately, these reactions also failed to yield cycloisomerization product, and only the intermediate enyne **1.113** was recovered (Scheme 1.24).

Scheme 1.24



Zhang had reported that only *Z*-enynes undergo $[Rh(dppb)]^+$-catalyzed cycloisomerizations, so we decided to optimize the allylic alkylation step to preserve the *Z* stereochemistry of the starting substrate **1.117**. An excellent *cis*/*trans* ratio of greater than 95:5 was achieved in acetonitrile at –40˚C (Scheme 1.25). Toluene was a poor solvent for this reaction because the malonate ion was insoluble at –40˚C.

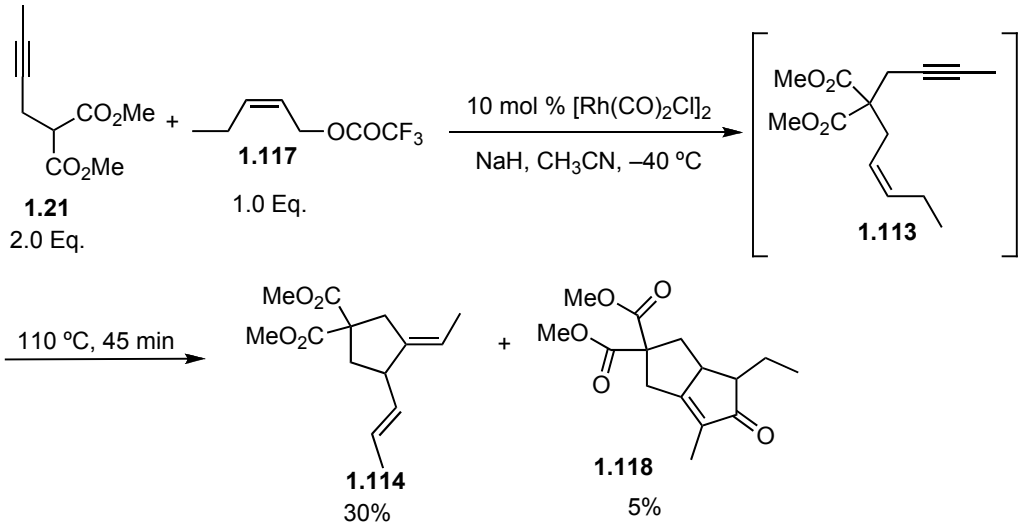
Scheme 1.25



Using these optimized conditions for the allylic alkylation step, the domino sequence proceeded in moderate yield for the first time, indicating that

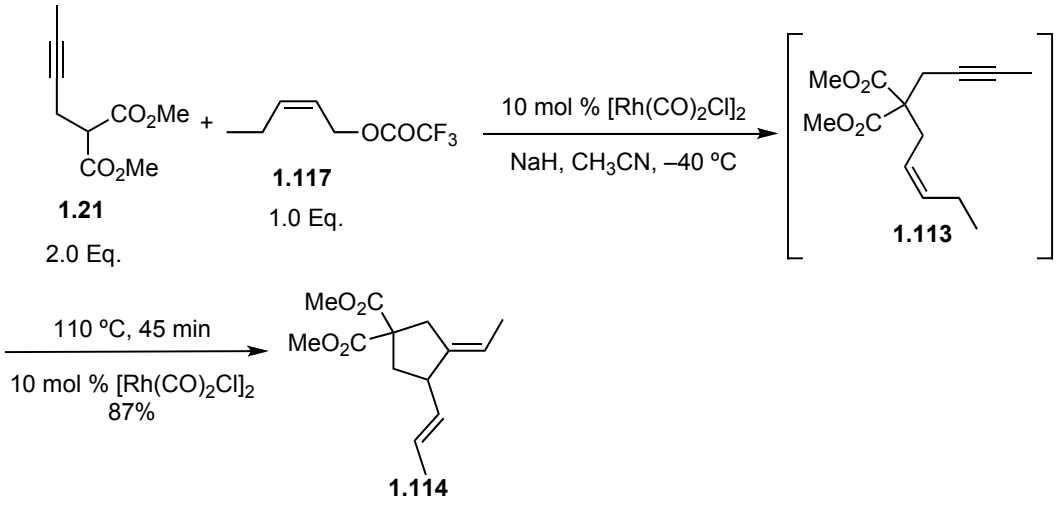
preservation of the *Z* stereochemistry was indeed crucial to the success of the reaction (Scheme 1.26). Along with a 30% yield of the desired product **1.114**, a minor amount of the Pauson-Khand product (**1.118**) was isolated, as well as a significant amount of the intermediate enyne **1.113**.

Scheme 1.26



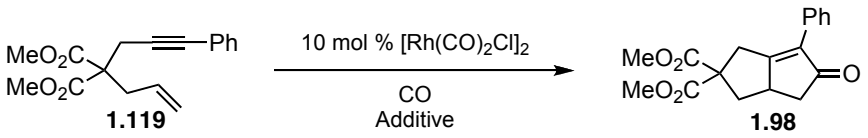
Doubling the catalyst loading did not increase conversion to the product, and extended heating times led to decomposition of the intermediate **1.113**. Interestingly, although doubling the initial catalyst loading did not lead to increased yield, adding an additional 10 mol% of catalyst before the second step led to a dramatic increase in yield (Scheme 1.27). This result indicated that the catalytic species resulting from the first catalytic cycle was altered in such a way as to be an inefficient catalyst for the second step.

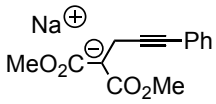
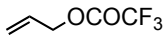
Scheme 1.27



The optimized reaction conditions for the allylic alkylation step included the use of excess malonate in order to achieve high yields of product. However, it seemed possible that while excess malonate was advantageous for the first catalytic cycle, it might be thwarting the second catalytic cycle, perhaps via coordination to the rhodium catalyst. Kenny Miller had also observed that the presence of malonate resulted in diminished yields in the $[Rh(CO)_2Cl]_2$-catalyzed Pauson-Khand reaction (Table 1.3, entry 2).

Table 1.3

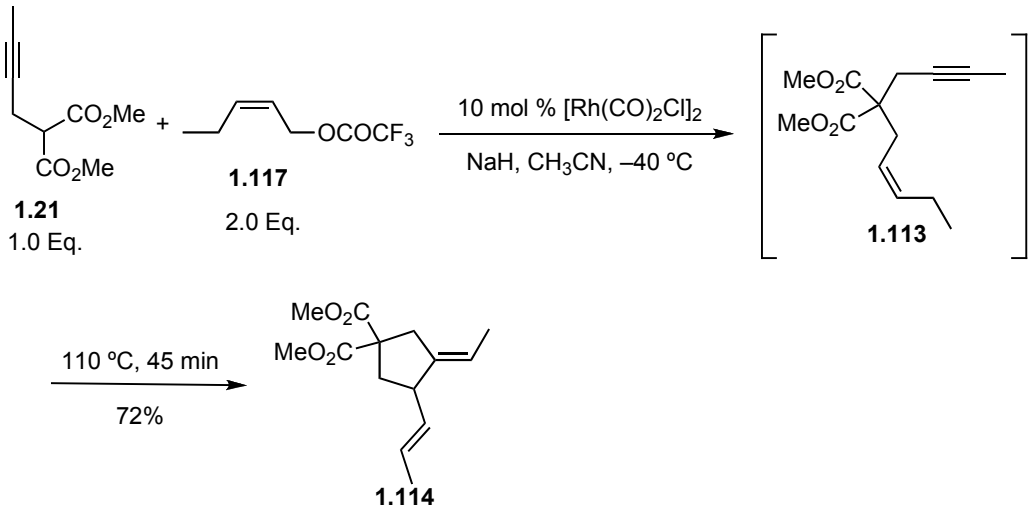


Entry	Additive	Yield
1	None	99
2		54
3		84

Miller, K.A. unpublished results

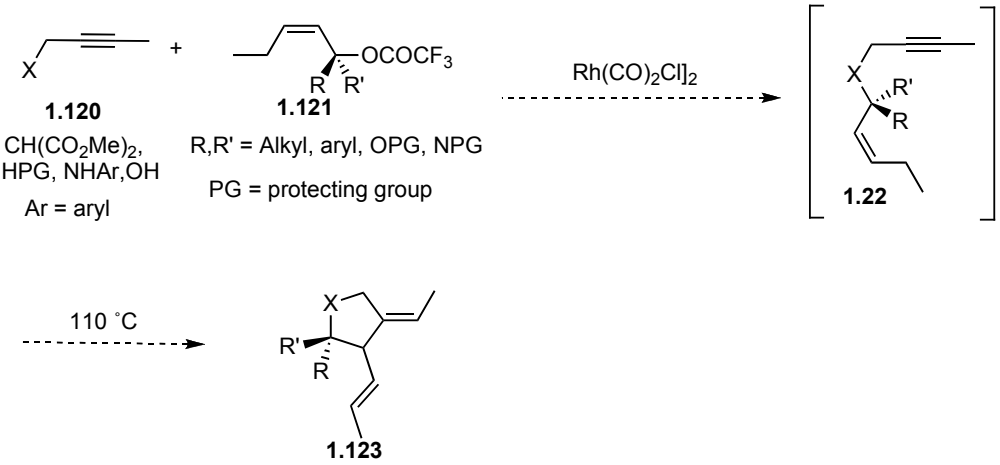
In order to limit the amount of malonate present in the reaction, the stoichiometry of the starting materials was inverted, and the allylic trifluoroacetate **1.117** was used in excess. In the event, the entire domino reaction proceeded in 72% yield with only 10 mol% catalyst (Scheme 1.28).[29] A range of stoichiometric equivalencies was screened, and the highest yield (72%) was obtained by using a two to one ratio of the trifluoroacetate to the malonate, thus confirming that the presence of excess malonate does indeed inhibit the cycloisomerization.

Scheme 1.28



Although **1.114** had not been previously synthesized, similar compounds have been synthesized via transition metal-mediated enyne cycloisomerizations from the corresponding 1,6-enynes.[20, 31, 32] Enyne cycloisomerization is the most frequently utilized synthetic approach to compounds of this type due to the extraordinary efficiency of the reaction. Our approach represents the first tandem allylic alkylation/cycloisomerization sequence used to synthesize vinyl alkylidene cyclopentanes. Although the first step could have been achieved via a simple S_N2 reaction (Scheme 1.20), this sequence has potential for application to substrates such as **1.120**, that would not be amenable to classical substitutions (Scheme 1.29). Furthermore, the ability of $[Rh(CO)_2Cl]_2$ to preserve *Z* stereochemistry in the allylic alkylation step is critical because a *Z*-enyne is required for efficient cycloisomerization. Because many transition metal catalysts isomerize double bonds in allylic alkylations, the use of our method for the construction of vinyl alkylidene cyclopentanes is advantageous.

Scheme 1.29

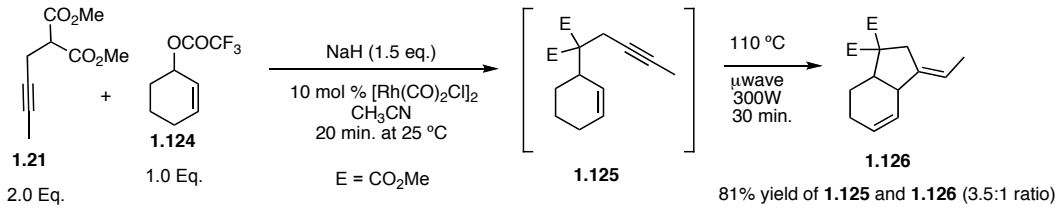


In addition to the efficient synthesis of **1.114**, the importance of this results is underscored by the fact that there are few examples of the promotion of sequential, mechanistically-distinct reactions by a single transition metal catalyst.[11] Furthermore, the absence of additives and ligands contributes to the operational simplicity of this methodology.

1.9.2 Accessing Bicyclic Compounds

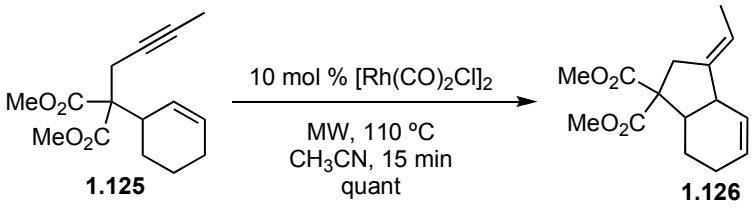
The success of this reaction led us to explore synthetic variations that would allow access to other core structures. The formation of fused bicyclic compounds *via* tandem allylic alkylation/cycloisomerization was investigated with the allylic trifluoroacetate **1.124** and propargylic malonate **1.21**. As was observed with the domino sequence to furnish **1.114**, an excess of the malonate led to incomplete conversion of intermediate enyne **1.125** to the desired product **1.126** (Scheme 1.30).

Scheme 1.30



In an effort to determine the efficiency of the second step, the enyne cycloisomerization was examined separately. In the event, it was found that the desired bicyclic adduct could be obtained in quantitative yield as a single isomer after heating at 110 ºC in only 15 minutes (Scheme 1.31).

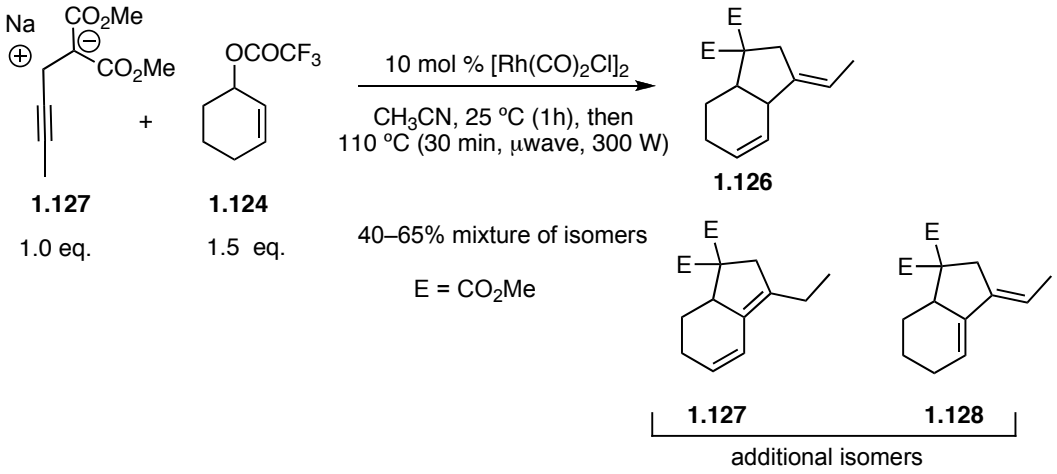
Scheme 1.31



In trials using an excess of the trifluoroacetate, the yields of the bicyclic product were found to be highly sensitive to the stoichiometric ratio of the allylic trifluoroacetate **1.124** to the propargylic malonate **1.21**; the optimum ratio was 1.5:1.0 (Scheme 1.32).[33] Although the desired product was always the major product, double bond isomers were invariably isolated. The use of microwave heating minimized the amount of additional isomers, but not completely. A range of heating times ranging from 4 hours to 15 minutes was explored in an attempt to minimize isomerization. Although the yield did not decrease with shortened reaction times, neither did the number of isomers produced. Reaction times less

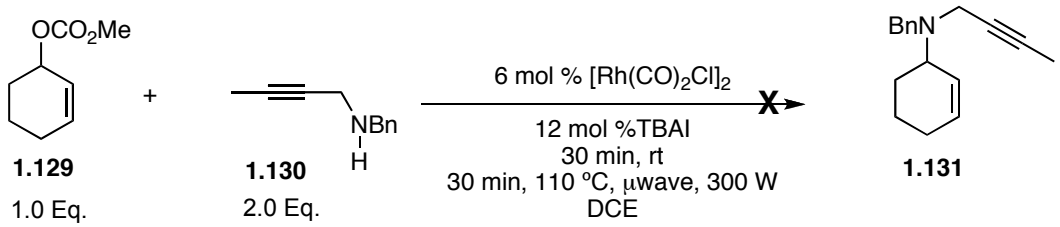
than 30 minutes resulted in greatly diminished yields, as did performing the reaction at lower temperatures.

Scheme 1.32



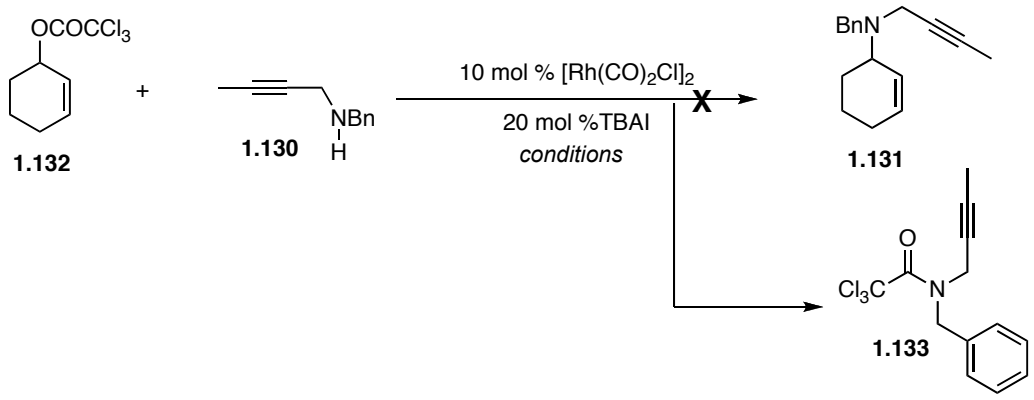
In an effort to access heterocyclic fused bicycles, it was desirable to examine the use of heteroatom-nucleophiles with allylic trifluoroacetate **1.124**. Towards that end, the reaction of propargylamine **1.130** with **1.129** was first studied (Scheme 1.33). Tetrabutylammonium iodide (TBAI) was used as an additive based upon work performed by Kenny Miller, who found that TBAI was necessary to avoid complexation of the amine with the rhodium catalyst. Despite the use of forcing conditions, none of the desired product **1.131** was obtained. Instead, an 86% yield of recovered carbonate **1.129** was isolated.

Scheme 1.33



When the allylic alkylation was attempted with the corresponding allylic trichloroacetate **1.132** and propargylamine **1.130** in a variety of solvents, none of the desired product was obtained. Rather the trichloroacetamide **1.133** was consistently obtained in 36% to 52% yields (Table 1.4). This product presumably arises from nucleophilic addition of the amine to the carbonyl group of the trichloroacetate, followed by loss of 2-cyclohexen-1-ol. Kenny Miller had also observed similar side-products in allylic aminations with allylic trifluoroacetates.

Table 1.4



Entry	Solvent	Conditions	Yield(%) of **1.131**	Yield(%) of **1.133**
1	THF	30 min at 23 ºC, then 30 min at 110 ºC (μwave, 300W)	0	39
2	CH_3CN	30 min at 23 ºC, then 30 min at 110 ºC (μwave, 300W)	0	52
3	PhMe	30 min at 23 ºC, then 30 min at 110 ºC (μwave, 300W)	0	36
4	CH_3CN	65 ºC (oil bath), 3 d	0	42

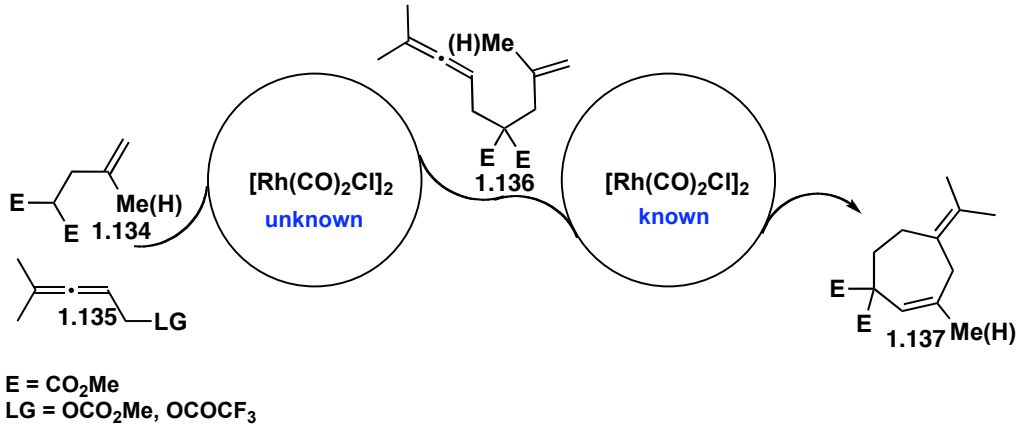
The incompatibility of heteroatom-nucleophiles with the allylic alkylation of cyclic allylic trifluoroacetates, as well as the 40-65% yields observed for the domino sequence furnishing **1.126**, indicate that this method is not the ideal synthetic approach to fused bicycles. Due to the lack of success in this area, further investigations with cyclic allylic substrates were not pursued.

1.9.3 Allenic Alkylation/Cycloisomerization Sequences

In light of Itoh's findings, an allenic alkylation/cycloisomerization domino sequence was envisioned that would convert allenes into medium-sized rings in

one pot (Figure 1.4). As allenic alkylations had not been reported with $[Rh(CO)_2Cl]_2$, the development of such chemistry would also broaden our existing allylic alkylation methodology. Hence the first task was to develop conditions for the $[Rh(CO)_2Cl]_2$–catalyzed allylic alkylation of allenic substrates.

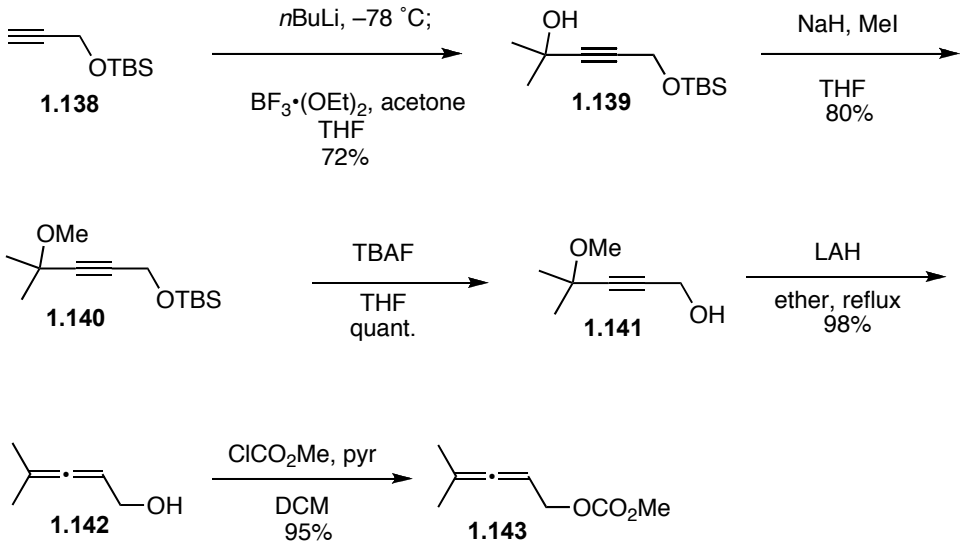
Figure 1.4



E = CO_2Me
LG = OCO_2Me, $OCOCF_3$

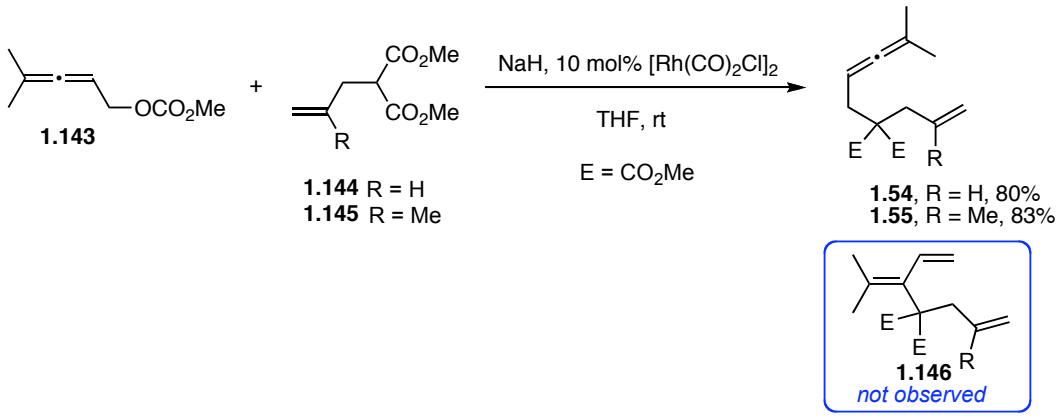
Allenic alcohol **1.142** was first made according to known literature procedures in four steps from the TBS-protected propargyl alcohol **1.138** (Scheme 1.34). [34] Allenic carbonate **1.143** was formed in 95% yield by reaction of **1.142** with methylchloroformate in pyridine and DCM.

Scheme 1.34



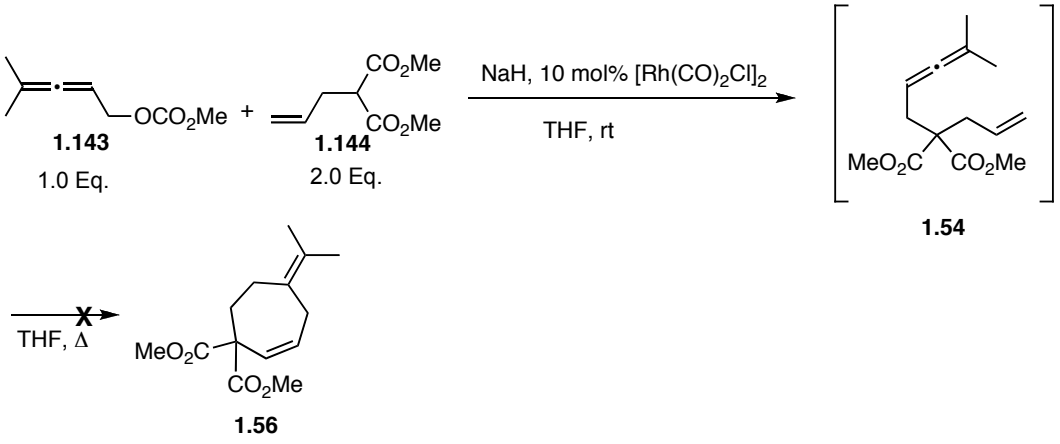
$[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of allenic carbonate **1.143** with malonates **1.144** and **1.145** proceeded smoothly to provide the corresponding allenenes **1.130** and **1.131** in 80% and 83% yields respectively (Scheme 1.35). Gratifyingly, regioisomer **1.146** was not isolated.

Scheme 1.35



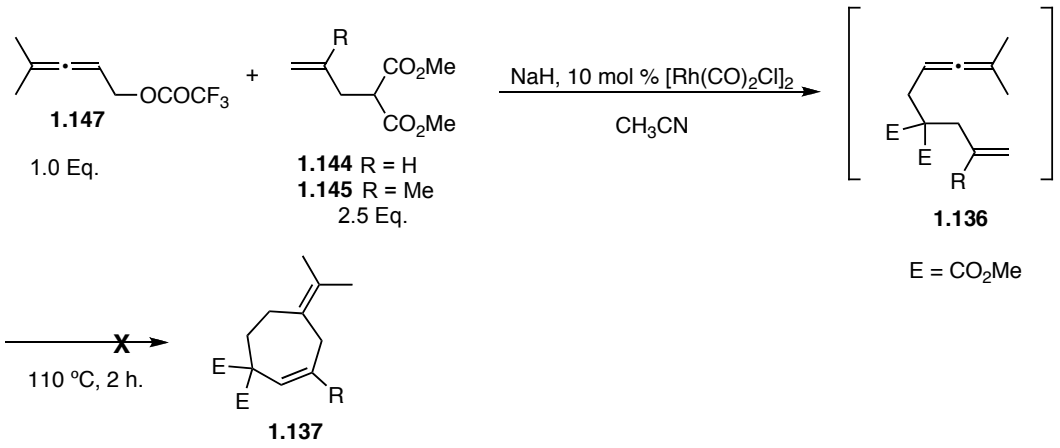
The domino sequence was attempted with the allenic carbonate in refluxing THF, but only the intermediate allenene **1.54** was recovered (Scheme 1.36).

Scheme 1.36



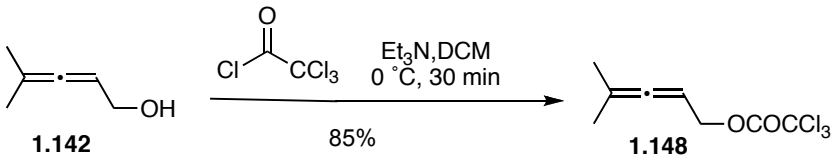
Based upon our prior success with allylic trifluoroacetates, the allenic trifluoroacetate **1.147** was employed as a substrate. The trifluoroacetate **1.147** was unstable and could not be purified, so the crude material was used. The solvent was changed to acetonitrile, and the reaction was heated to 110 °C in a sealed vial, but the domino sequence did not furnish the desired product **1.137** (Scheme 1.37). Additionally, the malonates **1.144** and **1.145** were the only materials recovered from the reaction. When the allylic alkylation of **1.147** with **1.145** was attempted separately, the allenene **1.55** was isolated in 44% yield.

Scheme 1.37



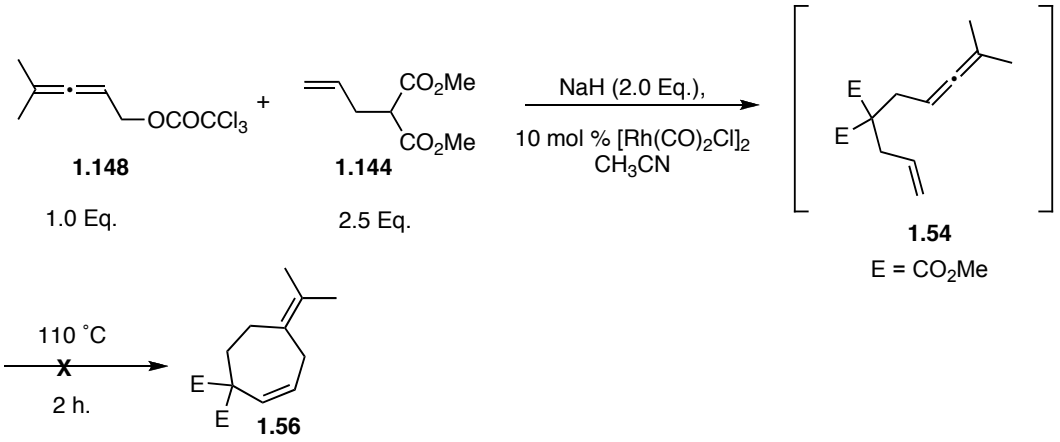
In consideration of the instability of the allenic trifluoroacetate **1.147** to purification, as well as the modest yield obtained in the allylic alkylation step, we explored the use of other allenic substrates. Because carbonate leaving groups had inhibited other domino sequences, we sought to use a leaving group that was electronically similar to the trifluoroacetate group. Towards that end, allenic trichloroacetate **1.148** was identified and prepared in 85% yield from the corresponding allenic alcohol **1.142** in the presence of triethylamine and trichloromethylchloroformate (Scheme 1.38).

Scheme 1.38



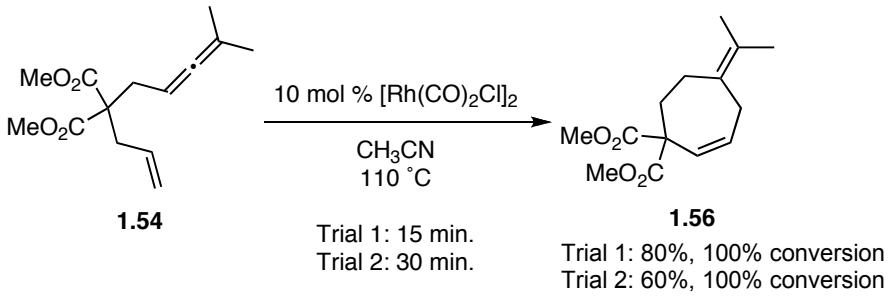
Using allenic trichloroacetate **1.148** and an excess of malonate **1.144**, the domino sequence was attempted, but only the intermediate allenene **1.54** and malonate **1.144** were both recovered in low mass balance (Scheme 1.39).

Scheme 1.39



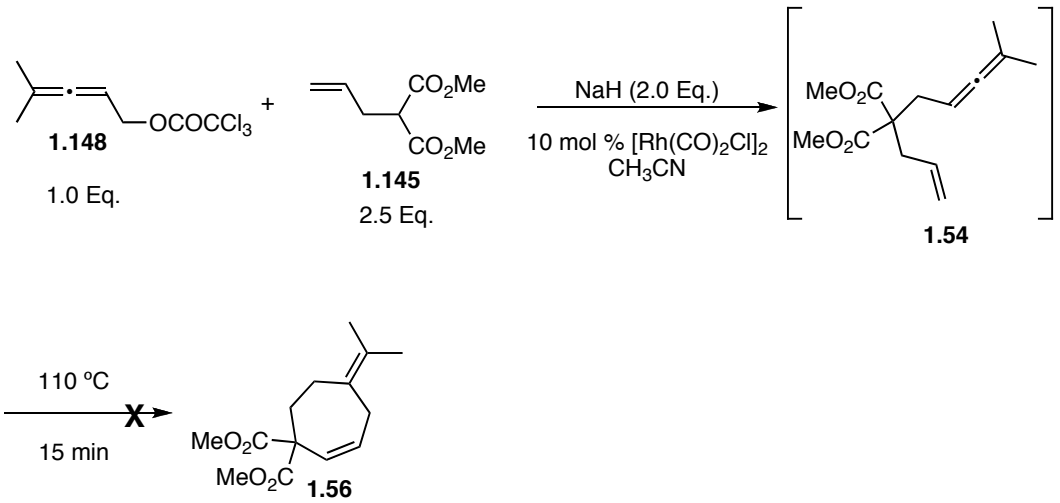
As we had not independently verified that the cycloisomerization reaction would proceed in acetonitrile at 110 ˚C, the cycloisomerization reaction was investigated separately. In the event, we found that cycloisomerization proceeded in acetonitrile at 110 ˚C in only 15 min to give **1.54** in 80% yield (Scheme 1.40).

Scheme 1.40



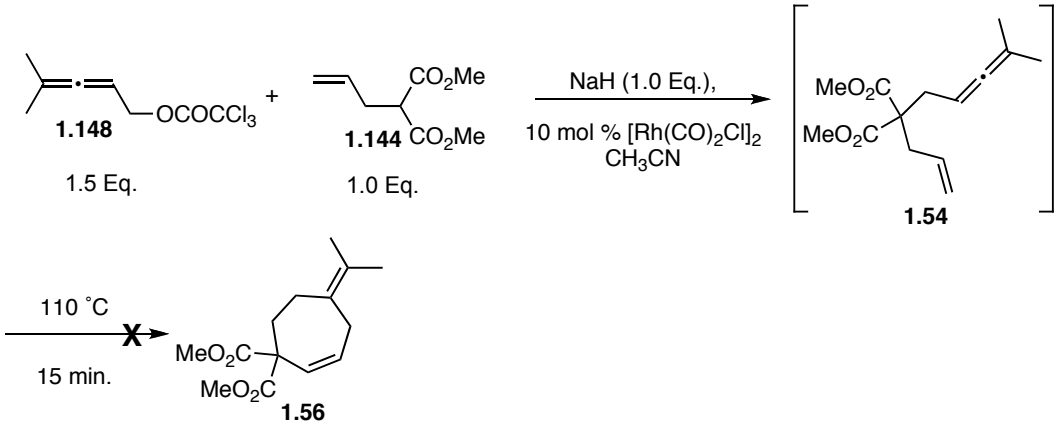
Based upon these findings, the allenic alkylation/cycloisomerization domino sequence was again attempted with abbreviated heating times (Scheme 1.41). However, none of the desired product **1.56** was isolated.

Scheme 1.41



In consideration of our earlier findings that the use of excess malonate inhibited the allylic alkylation/enyne cycloisomerization, the domino sequence was attempted with an excess of the allenic trichloroacetate (Scheme 1.42). However, the desired product was not isolated.

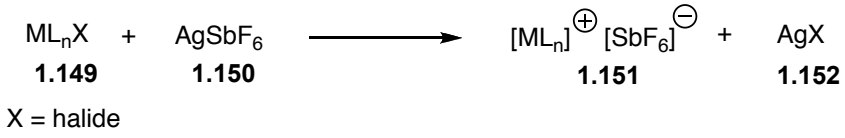
Scheme 1.42



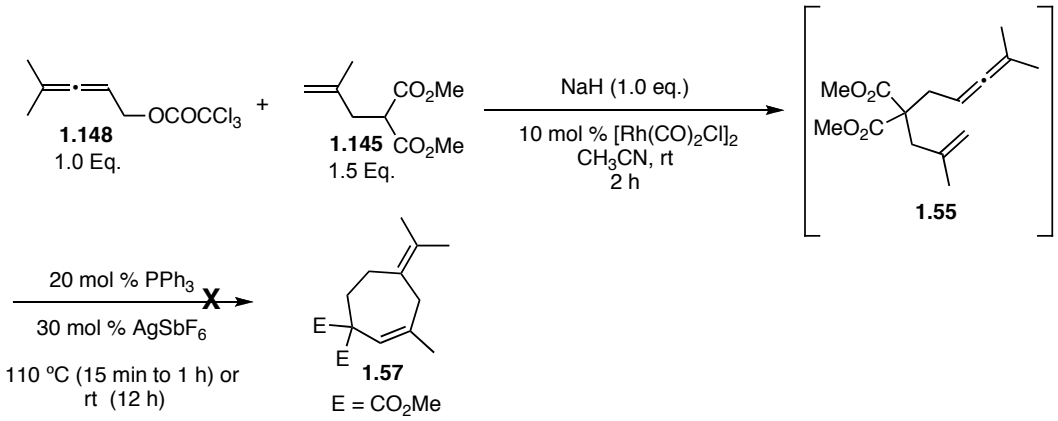
Based upon Zhang's report that cationic rhodium catalysts are effective promoters of enyne cycloisomerization, we explored the generation of a cationic

species from $[Rh(CO)_2Cl]_2$. Cationic transition metal species are often generated by the abstraction of a halogen atom from a neutral metal catalyst, with the assistance of a silver salt (Equation 1.1). The generation of a cationic metal species is facilitated by electron-rich ligands that stabilize the resultant positive charge. However, $[Rh(CO)_2Cl]_2$ is a poor candidate for such a transformation due to the electron-withdrawing nature of the CO ligands. However, a simple ligand exchange, in which the CO ligands are replaced by phosphine ligands, can easily remedy this problem. Thus, in order to generate a cationic rhodium species from $[Rh(CO)_2Cl]_2$, triphenylphosphine and the silver salt were sequentially added. As there is no need for a cationic species in the first step of the domino sequence, initial experiments were performed in which the triphenylphosphine and silver hexafluoroantimonate were added immediately before the cycloisomerization step. However, these conditions only led to a low recovery of the starting malonate and intermediate allenene (Scheme 1.43).

Equation 1.1

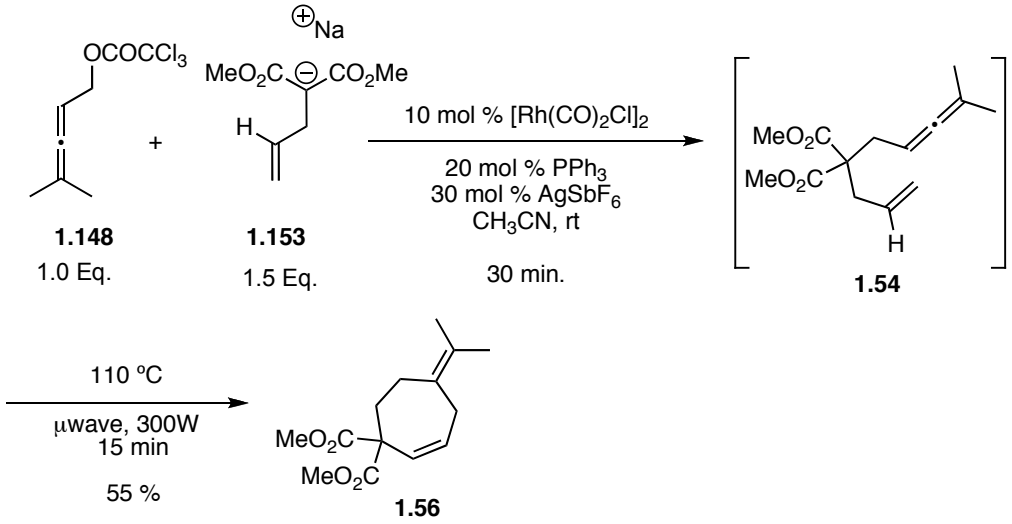


Scheme 1.43



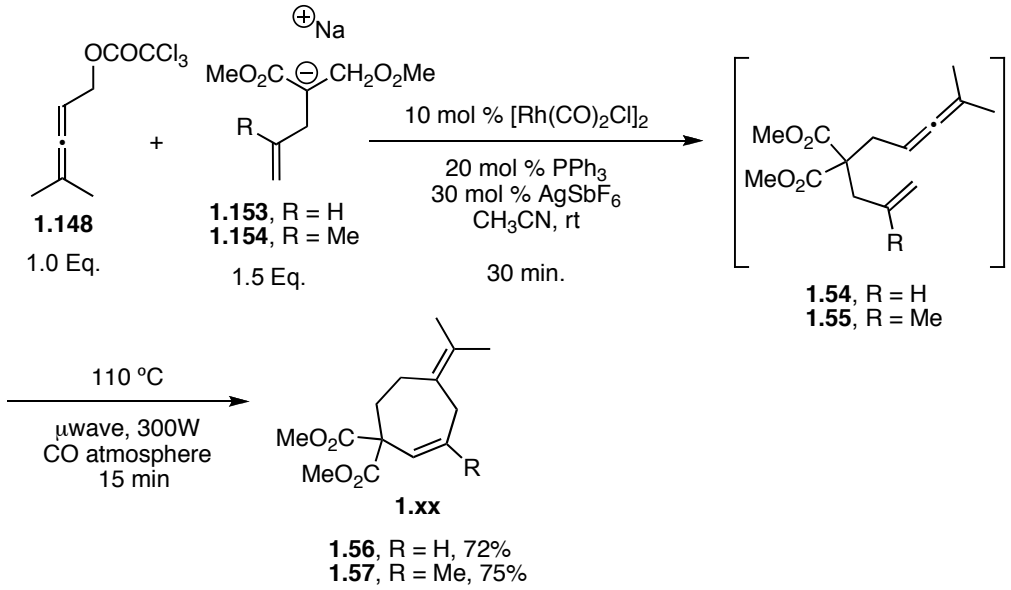
Variations on the timing of the addition of the phosphine ligand and silver salt were examined. When triphenylphosphine was added prior to the allylic alkylation and $AgSbF_6$ was added prior to the cycloisomerization, none of the desired product was isolated. However, when both the ligand and silver salt were added in the first step a 55% yield of the desired product was isolated (Scheme 1.44). Heating in the microwave led to slightly increased yields, relative to traditional heating.

Scheme 1.44



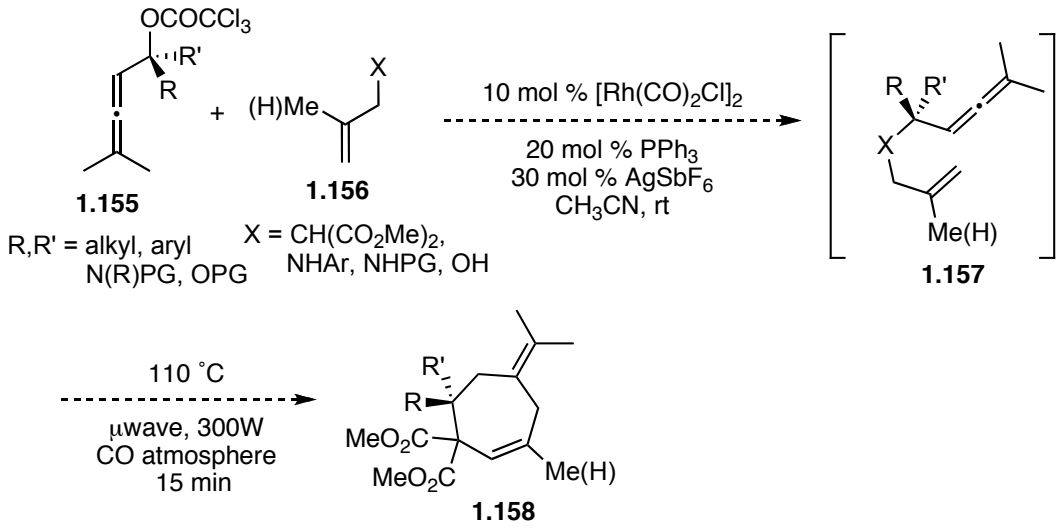
It was reported by Ito that slightly higher yields of allene-ene cycloisomerization products could be obtained under a carbon monoxide atmosphere rather than an argon atmosphere.[8] Accordingly, the domino sequence was conducted under a CO atmosphere and, to our delight, the desired products **1.56** and **1.57** were formed in 72% and 75% yields, respectively (Scheme 1.45). Interestingly, no Pauson-Khand side-products were isolated from this sequence.

Scheme 1.45



Although neither **1.56** nor **1.57** have been elaborated to natural products, unsaturated seven-membered rings are found in numerous sesquiterpenoid and diterpene natural products, making the efficient construction of such rings an important undertaking.[1] The tandem allenic alkylation/cycloisomerization sequence offers an atom economical approach to medium-sized carbocycles and has the potential for elaboration to heterocycles with the employment of heteroatom-nucleophiles. Although the sequence to furnish **1.56** and **1.57** could also be performed efficiently in two steps using a classical substitution reaction rather than an allylic alkylation as the first step, the domino sequence would be particularly useful with allenic substrates such as **1.155,** for which substitution via classical methods would be impossible (Scheme 1.46).

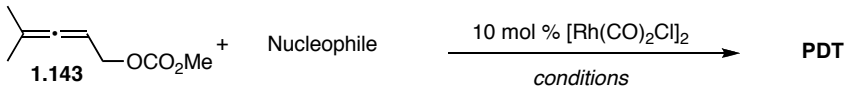
Scheme 1.46



1.9.4 Allenic Alkylations with Heteronucleophiles

The compatibility of heteronucleophiles with allenic substrates in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations was examined with allenic carbonate **1.143** and several heteronucleophiles, including pyrrolidine, benzylamine, *N*-methylaniline, and *o*-phenylphenol (Table 1.5). Although the reactions with pyrrolidine and benzylamine did not give the desired products, the reaction of *N*-methylaniline with allenic carbonate **1.143** produced the aniline **1.164** in 99% yield and >95:5 regioselectivity (Table 1.5, entry 3). To our further delight, it was discovered that *o*-phenylphenol **1.165** also reacted with allenic carbonate **1.143** to furnish **1.166** in 75% yield and >95:5 regioselectivity (Table 1.5, entry 4).[33]

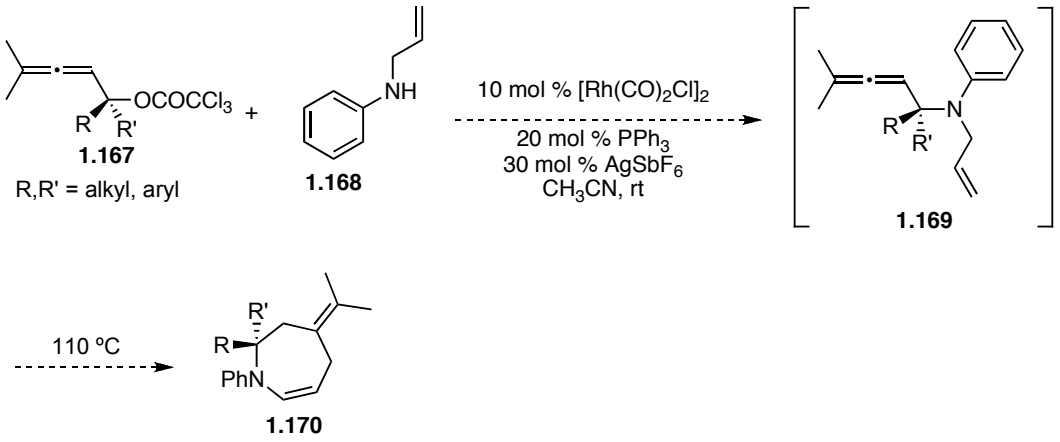
Table 1.5



Entry	Nucleophile	Conditions	PDT	Yield(%)
1	$BnNH_2$ **1.159**	TBAI,18 h, 25 ºC CH_3CN	**1.160** NHBn	0
2	N H **1.161**	TBAI,18 h, 25 ºC CH_3CN	**1.162** N	0
3	Me NH **1.163**	TBAI,1h, 60 ºC CH_3CN	**1.164** N Me	99 >99:5 regioselectivity
4	H O **1.165**	LiHMDS, CuI 1 h, 60 ºC THF	**1.166** O	75 >99:5 regioselectivity

Although such substrates cannot be elaborated to cyclized products, if functionalized nucleophiles such as **1.168** were used, then medium-sized rings containing enamine functionality could be accessed with the tandem allenic alkylation/cycloisomerization sequence (Scheme 1.47). Although we did not pursue these reactions, we have established proof of principle for the viability of such Rh-catalyzed allenic alkylation/cycloisomerization tandem sequences.

Scheme 1.47



1.10 SUMMARY AND CONCLUSIONS

Several novel $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/cycloisomerization tandem sequences were developed that access complex molecules from simple starting materials in one pot. Both the allylic alkylation/enyne cycloisomerization and allenic alkylation/cycloisomerization tandem sequences are unprecedented.

The success of the domino sequences was dependent upon the nature of the allylic substrate, failing when allylic or allenic carbonates were employed. The reason for this may be due to an interaction between the carbonate and the rhodium catalyst, altering its reactivity such that it cannot promote the subsequent catalytic cycle. This problem was overcome by using allylic trifluoroacetates or, in the case of allenic substrates, using allenic trichloroacetates.

The stoichiometry of the malonate and allylic substrate proved to be greatly important in the allylic alkylation/enyne cycloisomerization sequence, with excess malonate resulting in significantly diminished yields of cycloadducts.

By using an excess of the allylic trifluoroacetate, a good yield of the desired adduct could be attained. Cyclic allylic substrates are much less amenable to allylic alkylation with $[Rh(CO)_2Cl]_2$, in comparison to their acyclic counterparts. This observation is consistent with Takeuchi's reports using iridium catalysts and indicates that this methodology is not the ideal synthetic approach to fused bicyclic compounds.

The allenic alkylation/cycloisomerization sequence necessitated the formation of a cationic rhodium catalyst *in situ*, but led to good yields of medium-sized rings under an atmosphere of carbon monoxide. Novel allenic alkylations were established that proceed with excellent regioselectivity and yields. In addition to stabilized carbon nucleophiles, oxygen and nitrogen nucleophiles are amenable to the alkylation of allenes. These results not only broaden the scope of our $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation methodology, but also establish proof of principle for the viability of allenic alkylation/cycloisomerization sequences to furnish heterocycles.

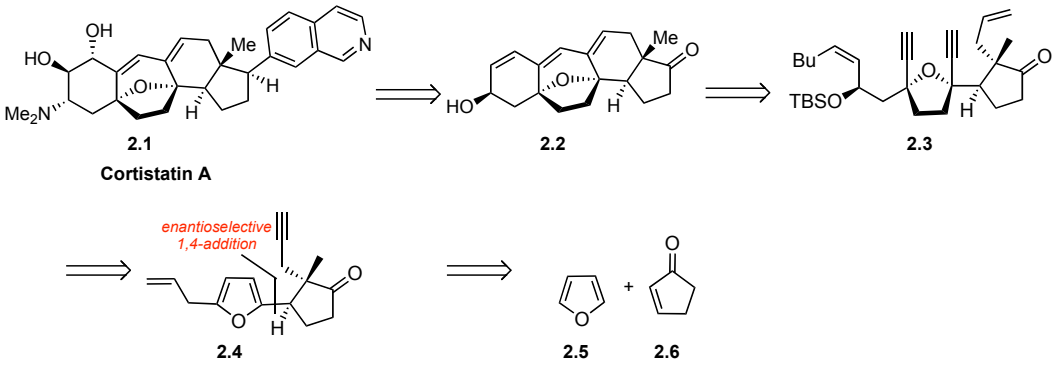
The possibilities of using the established domino sequences with diverse allylic compounds and nucleophiles are numerous. Such sequences could be applied to the concise synthesis of a variety of cyclic scaffolds. In addition, such tandem processes are often used in library synthesis and the incorporation of these reactions into a library synthesis could lead to a diverse array of functionally dense, small molecules.

Chapter 2: Enantioselective Conjugate Addition Employing 2-Heteroaryl Nucleophiles

2.1. INTRODUCTION

In the context of ongoing efforts in the Martin Group towards the total synthesis of cortistatin A, it was necessary to add a furan-2-yl nucleophile enantioselectively to 2-cyclopenten-1-one via a 1,4-addition (Scheme 2.1). However, at the time this work was initiated, there were no known reports of such a transformation. Indeed, there were no reported methods for the enantioselective 1,4-addition of any 2-heteroaryl nucleophiles to Michael acceptors, despite the wide prevalence of heteroaromatic compounds in drug-like molecules and the general utility that such a method would offer to both synthetic and medicinal chemists.

Scheme 2.1

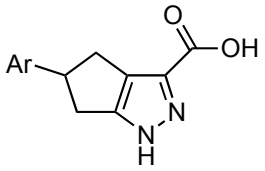


The establishment of such a method would be applicable not only to the Martin Group's synthesis of cortistatin A, but to a number of other biologically relevant molecules as well, such as Merck & Co.'s recently patented series of

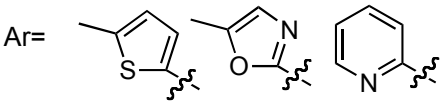
niacin receptor agonists (Figure 2.1).[35] These compounds are potential drugs for the treatment of dyslipidemias, diseases resulting from high cholesterol levels.

Figure 2.1

Niacin agonists

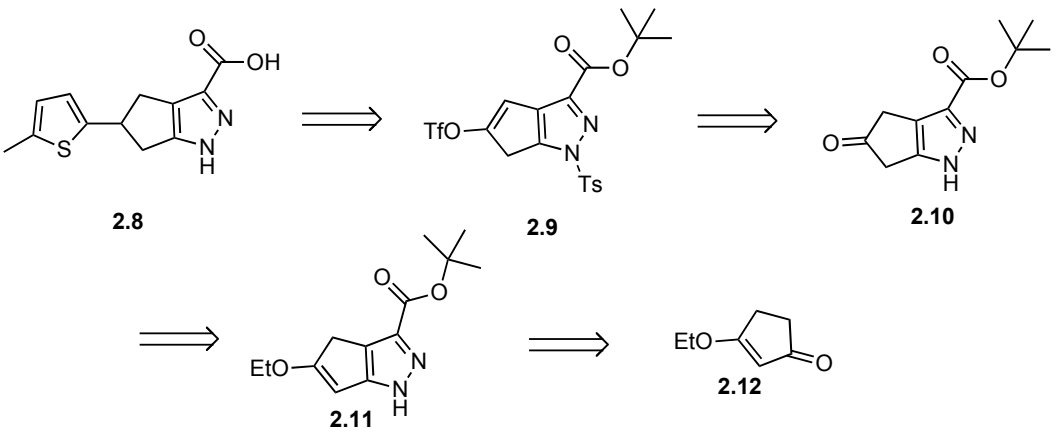


2.7



These compounds are currently synthesized as racemic mixtures via multi-step syntheses. Merck's synthetic route to pyrazole **2.8** consists of eight steps with the thiophene introduced via a late stage Suzuki coupling (Scheme 2.2).

Scheme 2.2

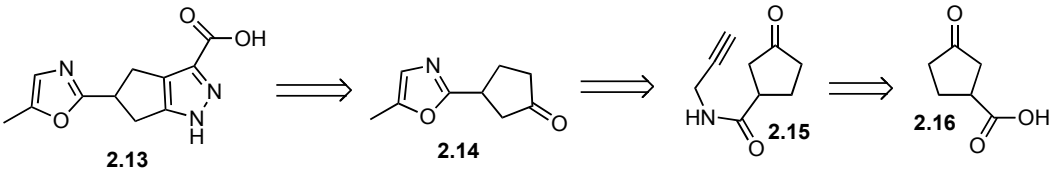


2.8 **2.9** **2.10**

2.11 **2.12**

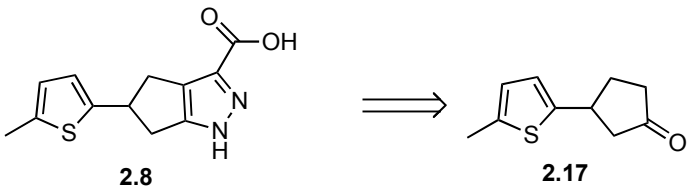
In the case of oxazole-substituted pyrazole **2.13**, the synthetic sequence is much shorter and proceeds through a 3-(5-methyloxazol-2-yl)cyclopentanone intermediate **2.14** (Scheme 2.3).

Scheme 2.3



If it were possible to add a thiophen-2-yl nucleophile enantioselectively to 2-cyclopenten-1-one, then the 3-(5-methylthiophene-2-yl)cyclopentanone intermediate **2.17** could be accessed in only one step. By employing the same final step used by Merck to synthesize pyrazole **2.13** from intermediate **2.14**, both enantiomers of **2.8** could be accessed in only two steps (Scheme 2.4).

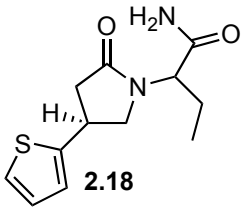
Scheme 2.4



In addition to Merck's niacin agonists, UCB patented **2.18**, an anticonvulsant with applications in treating neurological disorders such as epilepsy. The structure contains a β-thiophen-2-yl lactam, which could be accessed via an enantioselective 1,4-addition of thiophene to a five-membered unsaturated lactam (Figure 2.2).[36]

Figure 2.2

Anticonvulsant



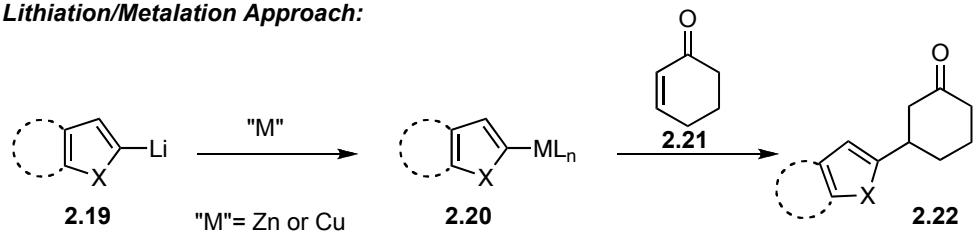
2.18

2.2 RACEMIC CONJUGATE ADDITION METHODOLOGIES EMPLOYING HETEROAROMATIC NUCLEOPHILES

Two dominant approaches to adding heteroaromatic nucleophiles to enones have been reported in the literature. The first approach involves lithiation of the heteroaromatic compound followed by transmetallation to a metal, usually zinc or copper (Scheme 2.5). The newly formed organometallic reagent is then added to a Michael acceptor, with or without the assistance of a Lewis acid. The second approach is simply a classical Friedel-Crafts alkylation and requires the assistance of a Lewis acid (Scheme 2.6).

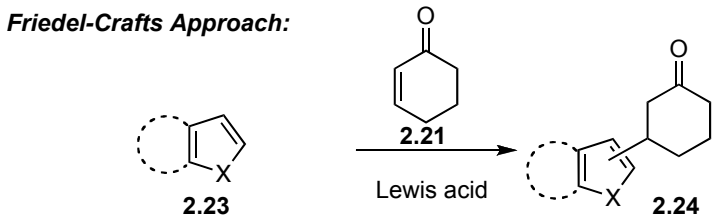
Scheme 2.5

Lithiation/Metalation Approach:



2.19 **2.20** **2.22**

Scheme 2.6

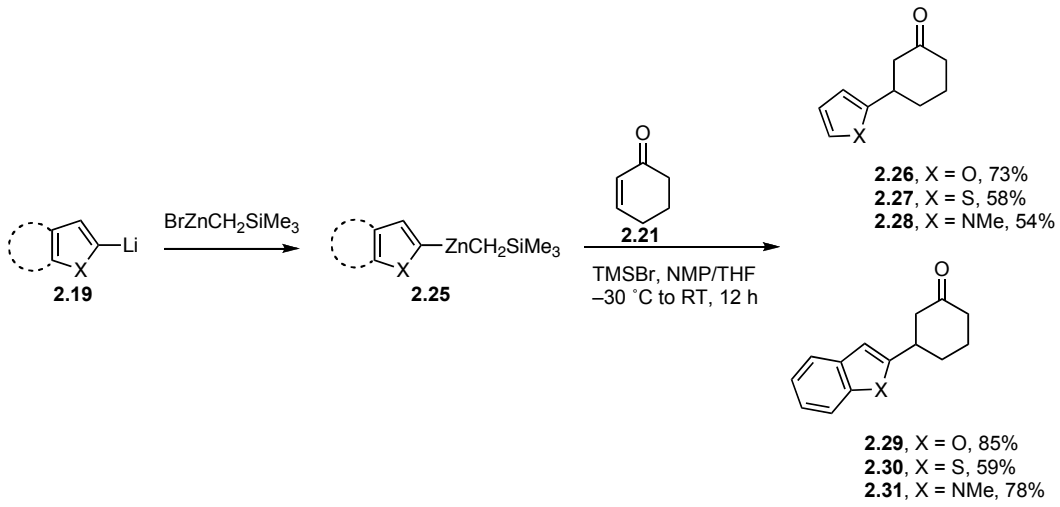


2.2.1 Lithiation/Metalation Approach

There are several reports that apply the lithiation/metalation approach to the racemic 1,4-addition of heteroaromatic nucleophiles to Michael acceptors. Lipshutz has added higher order furan-2-yl cyanocuprates, which were prepared from 2-lithiofuran and copper cyanide, to 5- and 6-membered enones, achieving moderate yields of products.[37]

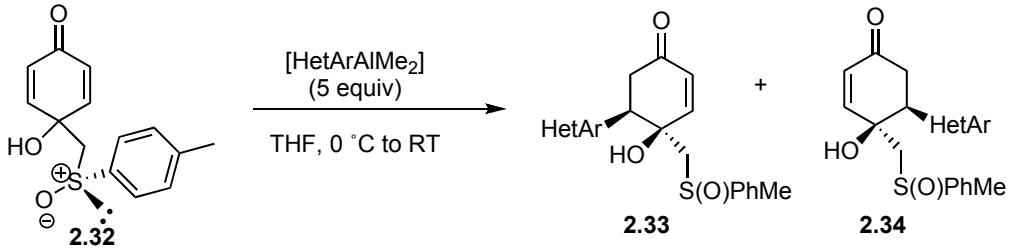
Knochel has reported a general method for the addition of mixed diorganozincs to 2-cylcohexen-1-one, in the presence of TMSBr.[38] The heteroaromatic nucleophiles are prepared by lithiation at the 2-position and subsequent transmetallation to trimethylsilylmethylzinc bromide. A variety of 2-heteroaryl nucleophiles can be used, including pyrrol-2-yl, thiophen-2-yl, furan-2-yl, indol-2-yl, benzothiophen-2-yl, and benzofuran-2-yl zinc compounds (Scheme 2.7).

Scheme 2.7

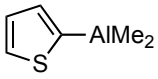
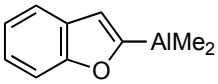
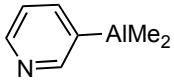


Although no enantioselective variants of the lithiation/metalation approach exist, Ribagorda and coworkers have reported two examples of a diastereoselective 1,4-addition of 2-heteroaryldimethylaluminum nucleophiles to the meso, pro-chiral cyclohexadienone derivative **2.32**.[39] The aluminum compounds are prepared via lithiation of the corresponding heteroaryl compound and subsequent *in situ* transmetallation to aluminum with $AlMe_2Cl$. Using this method, both benzofuran-2-yl- and thiophen-2-ylaluminum reagents were added to compound **2.32** in good yield and modest diastereomeric ratio (4:1) (Table 2.1, entries 1 and 2). In the case of the pyrid-3-ylaluminum substrate **2.37**, both the yield and diastereomeric ratio were poor (Table 2.1, entry 3). One limitation of this method is that five equivalents of the nucleophile are required to achieve optimum results.

Table 2.1



2.32 **2.33** **2.34**

Entry	$HetArAlMe_2$	Yield (%)	dr (ratio of **2.33**:**2.34**)
1	 **2.35**	90	4:1
2	 **2.36**	75	4:1
3	 **2.37**	20	3:2

2.2.2 Friedel-Crafts Approach

Furan compounds are also viable Friedel-Crafts partners, and the conjugate addition of furans to enones can be induced in the presence of a Lewis acid. Furan is a highly reactive nuclephile, which has historically been problematic in Friedel-Crafts alkylation reactions due to polymerization side-reactions that reduce product yields. More recent reports, however, indicate that this limitation can be overcome by simply using mild conditions.[40]

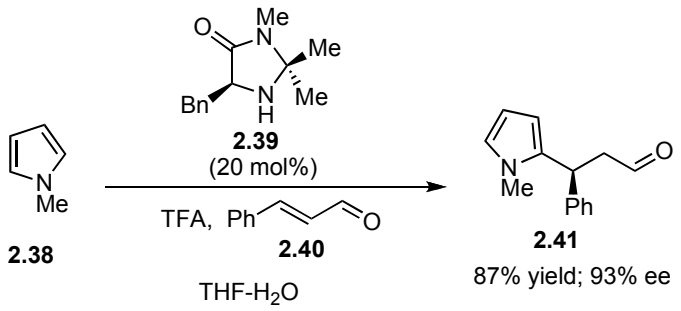
Kraus has reported the addition of furan derivatives to enones in the presence of stoichiometric TMSI.[41] One advantage of Kraus's method is that

either the silyl enol ether or ketone product can be selectively isolated, depending upon the workup conditions.

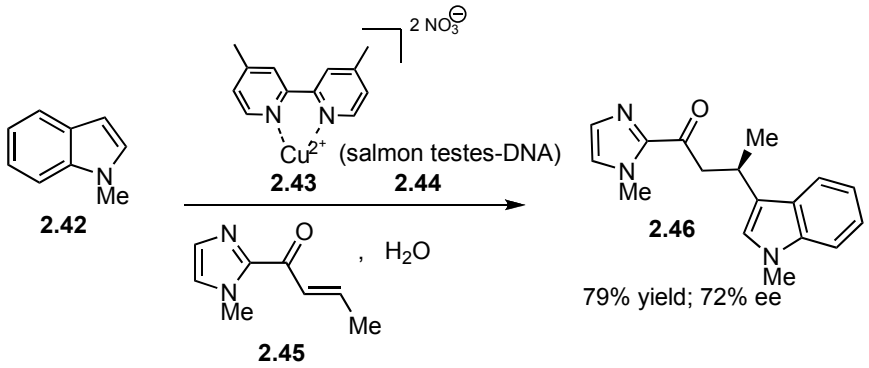
Heteroaromatic compounds other than furan have also been employed in Friedel-Crafts conjugate addition reactions. Indole, for example, has been widely used, but will preferentially react at the C3-position. Pyrrole, on the other hand, will react smoothly at the 2-position, as will thiophene.[42] Benzofuran and benzothiophene have not been reported to be effective partners in Friedel-Crafts reactions. Common reported problems with these Friedel-Crafts reactions include polyalkylation, polymerization, and low regioselectivity when two or more reactive sites are available.

A few enantioselective Friedel-Crafts methods have been published that utilize heteroaryl compounds.[43, 44] These methods limit the acceptor to either α,β-usaturated aldehydes (Scheme 2.8) or unsaturated 2-acyl imidazoles (Scheme 2.9) and the nucleophile scope is limited to pyrrole and indole. There are no examples of enantioselective Friedel-Crafts additions of 2-heteroaromatic compounds to simple enones.

Scheme 2.8



Scheme 2.9



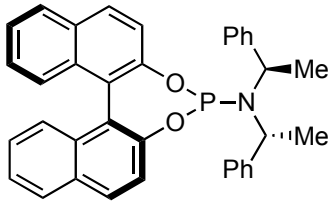
2.3 ENANTIOSELECTIVE CONJUGATE ADDITION EMPLOYING TRANSITION METAL CATALYSIS

To date the most promising work in the area of enantioselective conjugate addition has emerged from the field of transition metal catalysis. A variety of transition metals have been employed, including ruthenium, iridium, nickel, palladium, rhodium, and copper,[45] and as a result there are currently a large number of methods that produce enantioenriched β-alkyl and β-aryl carbonyl compounds. The methods most relevant to our synthetic goals have employed palladium and rhodium catalysts, although copper catalysts have been used to a lesser extent.

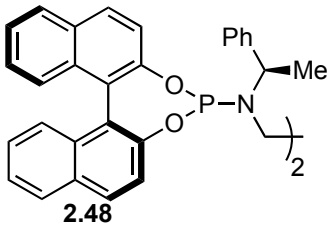
2.3.1 Copper Catalysis

The majority of the seminal work in the area of copper-catalyzed conjugate addition methodology has focused on dialkylzinc nucleophiles,[46-51] with far fewer reports using diphenylzinc nucleophiles.[52-54] Most of the prolific research in this area has been focused on ligand design, not on developing the nucleophile or acceptor scope, and has most frequently employed diethylzinc as the sole nucleophile and either chalcone or 2-cyclohexen-1-one as the sole acceptor. Of the several hundred ligands that have been developed to date, the most popular and successful ligands include Feringa's phosphoramidite ligands and Hoveyda's modular peptide ligands (Figure 2.3). Copper sources include a wide range of both Cu(I) and Cu(II) salts, with $Cu(OTf)_2$ being the most commonly employed.

Figure 2.3

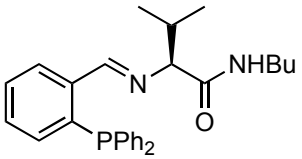


2.47

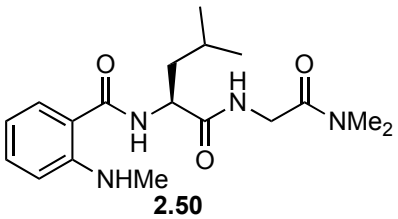


2.48

Representative Phosphoramidite Ligands



2.49



2.50

Representative Modular Peptide Ligands

Although much of the work reported in the area of Cu-catalyzed conjugate additions is limited to the use of dialkylzinc reagents, recent progress has been made in expanding the nucleophile scope to include aryl substrates. Towards that end, there are now several examples that employ diphenylzinc reagents, although the scope of the phenyl ring is still somewhat unexplored and there are no examples to date using heteroaromatic substrates. In this area, Hoveyda has successfully added diphenylzinc reagents to β-disubstituted 2-cylcohexen-1-one and 2-cyclohepten-1-one acceptors in high yields and excellent ee (Scheme 2.10) with the use of a chiral bidentate *N*-heterocyclic carbene silver complex **2.52** (Figure 2.4).[55] Although impressive, this method does have its limitations in that it is incompatible with 2-cyclopenten-1-one, a Michael acceptor that has a long history of being a challenging substrate for Cu-catalyzed 1,4-additions.

Scheme 2.10

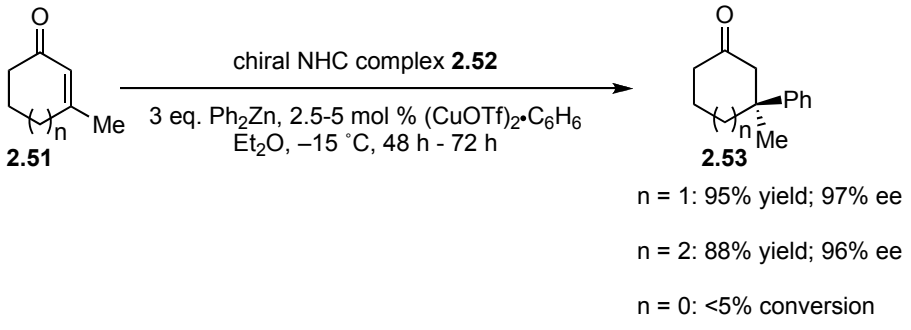
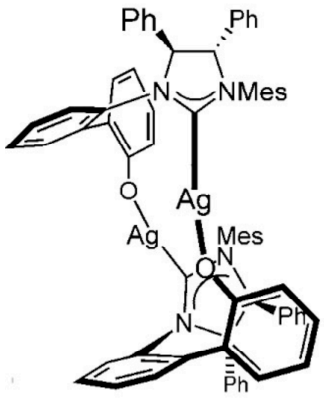


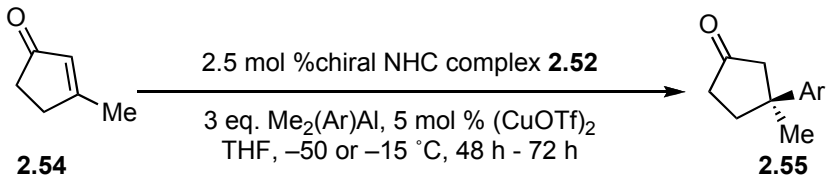
Figure 2.4



2.52

Recently, Hoveyda was able to overcome this limitation by using phenyl aluminum reagents instead of diphenylzinc,[56] which were prepared in the same way as Ribagorda's protocol.[39] These more reactive aryl nucleophiles were added to β-disubstituted 2-cyclopenten-1-one in moderate to high ee's and yields (Table 2.2).

Table 2.2

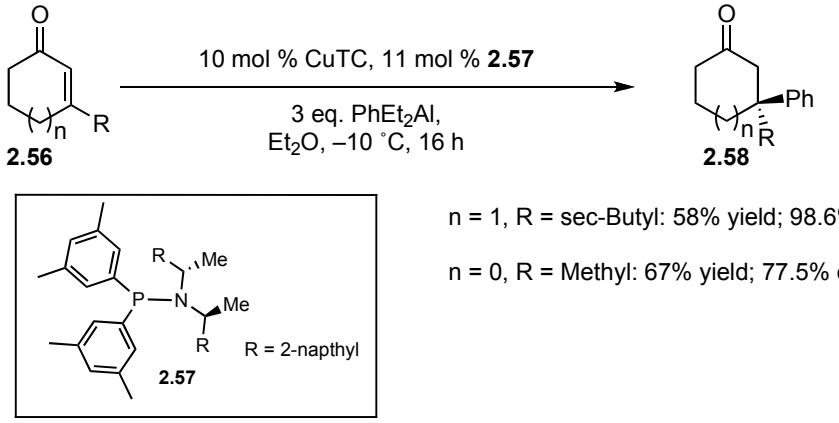


2.54 **2.55**

Entry	Ar	Yield (%)	ee (%)
1	C_6H_5	66	72
2	*o*-MeC_6H_4	85	98
3	*p*-$OMeC_6H_4$	67	71
4	*o*-$OMeC_6H_4$	55	95

Alexakis has recently published a similar method employing phenylaluminum reagents and a catalyst system derived from copper thiophenecarboxylate (CuTC) and the phosphoramidite ligand **2.57**.[57] Alexakis only reported one example of an aryl addition to 3-methylcyclopent-2-one. In the event, phenyldiethylaluminum was added in the presence of 10 mol % of CuTC and **2.57** to furnish the1,4-adduct in 67% yield and 77.5% ee (Scheme 2.11).

Scheme 2.11



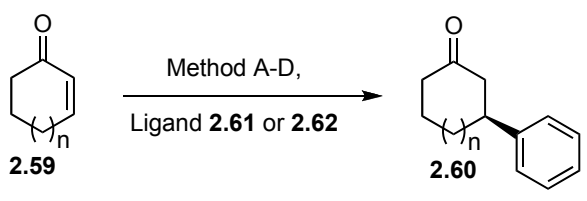
In addition to phenylzinc and phenylaluminum reagents, phenyl Grignard reagents have been employed with copper catalysts, albeit to a lesser degree and with limited nucleophile and electrophile scope.[58]

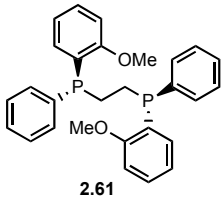
2.3.2 Palladium Catalysis

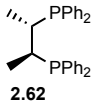
The palladium-catalyzed addition of aryl nucleophiles to 2-cyclopenten-1-one has been quite useful. Miyaura, the leader in this field, has successfully used dicationic benzonitrile palladium(II) complexes with a variety of aryl nucleophiles, including aryl boronic acids, aryl trifluoroborates, aryl bismuth, and aryl silicon reagents to achieve highly enantioselective 1,4-additions to a variety of enones (Table 2.3).[59, 60] In the case of triarylbismuths (method D), the active catalyst is a highly electrophilic nitrile-free catalyst, generated *in situ* in the presence of $Cu(BF_4)_2$, via ligand exchange of the benzonitrile and the copper salt. In the case of aryltrifluoroborates (method B), the addition of a copper salt is unnecessary to generate the active catalyst, because the BF_3 released in the reaction serves the same purpose. In contrast, aryl boronic acids are reactive

enough that a nitrile-free catalyst is not necessary. The presence of $AgBF_4$ in method A increases catalyst turnover and yields.[61] In all cases, water is used as a co-solvent.

Table 2.3







Entry	Method	n	Ligand	Yield (%)	ee (%)
1	A	0	**2.62**	94	94
2	B	0	**2.62**	60	95
3	C	0	**2.62**	84	94
4	D	0	**2.62**	85	95
5	A	1	**2.61**	90	92
6	B	1	**2.61**	95	93
7	C	1	**2.61**	83	92
8	D	1	**2.61**	92	92

A: $ArB(OH)_2$, $[Pd(L)PhCN)_2](SbF_6)_2$, $AgBF_4$, acetone-H_2O, 0 ˚C
B: $[ArBF_3]K$, $[Pd(L)PhCN)_2](SbF_6)_2$, MeOH-H_2O, –15→5 ˚C
C: $ArSiF_3$, $[Pd(L)PhCN)_2](SbF_6)_2$, ZnF_2, MeOH-H_2O, 0→5 ˚C
D: Ar_3Bi, $[Pd(L)PhCN)_2](SbF_6)_2$, $Cu(BF_4)_2$, MeOH-H_2O, –5→10 ˚C

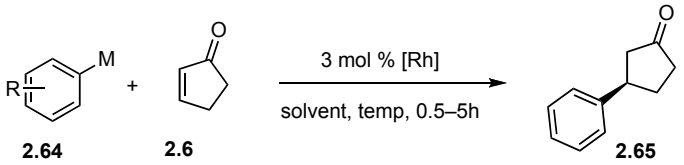
Minnaard and co-workers have used a catalyst derived from palladium trifluoroacetate and Me-DUPHOS to transfer a variety of electron-neutral and

electron-rich aryl boronic acids to enones.[62] Minnaard's method is also compatibile with 2-cyclopenten-1-one, furnishing adducts in 82% ee.

2.3.3 Rhodium Catalysis

The field of rhodium catalysis has produced the most relevant methods to our synthetic goals. In particular, Hayashi has used a variety of aryl sources, including aryl boronic acids, aryl titanium reagents, and arylzinc chlorides with a variety of Rh(I) catalysts (Table 2.4).[63-69] In all of Hayashi's examples, reactions with 2-cyclopenten-1-one proceeded in high yields and excellent ee's, far superior to both the copper- and palladium-catalyzed methods. In many cases, Hayashi has reported mild reaction conditions and short reaction times (ca. 30 min).

Table 2.4

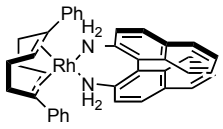


2.64 **2.6** **2.65**

R = H, 4-CF_3, 4-OMe

Entry	M	[Rh]	Temp.	Ar–M Eq.	Solvent	Yield (%)	ee (%)
1[a]	$B(OH)_2$	$[Rh(acac)(C_2H_4)_2]$/(*S*)-BINAP	100 ˚C	2.5	Dioxane/H_2O	93	97
2[a,b]	$B(OH)_2$	$[Rh(OH)$(*S*)-$BINAP]_2$	35 ˚C	2.5	Dioxane/H_2O	95	98
3[a,b,c]	$Ti(OiPr)_3$	$[Rh(OH)$(*S*)-$BINAP]_2$	20 ˚C	1.6	THF	56	>99
4[c]	$Ti(OiPr)_4Li$	$[RhCl(C_2H_4)_2]_2$/(*S*)-BINAP	20 ˚C	1.5	THF	83-94	96-99
5[a,b,c]	ZnCl	**2.63**	20 ˚C	1.5	THF	92	90

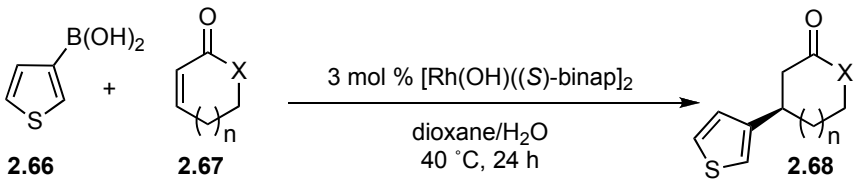
[a]Only PhH-M used (R=H only); [b]Glovebox required; [c] 1.5-2.0 eq. of TMSCl used



Catalyst 2.63

Hayashi has also reported the $[Rh(OH)$(*S*)-$BINAP]_2$-catalyzed addition of 3-thiopheneboronic acid to a variety of Michael acceptors (Table 2.5).[70] This was the first example of an enantioselective conjugate addition employing a heteroaromatic nucleophile. The major limitation of this reaction, however, is that the catalyst needed for this transformation is $[Rh(OH)$(*S*)-$BINAP]_2$, which is extremely air-sensitive, and the reaction must be performed in a glovebox.

Table 2.5



2.66 **2.67** **2.68**

Entry	X	n	Yield (%)	ee (%)
1	$-CH_2-$	0	78	97
2	$-CH_2-$	1	67	99
3	$-CH_2-$	2	81	99
4	O	1	79	99

Oi and coworkers found that organosiloxane nucleophiles add to a range of acyclic and cyclic enones, including 2-cyclopenten-1-one, in the presence of a cationic Rh(I)/BINAP complex.[71] Although this method has achieved high ee's and yields, it requires high temperatures and long reaction times.

2.4 OBSTACLES TO EMPLOYING 2-HETEROARYL COMPOUNDS

In light of the prolific research that has been performed in the area of enantioselective 1,4-additions of aryl compounds to enones it is perhaps surprising that very few examples have been reported in which heteroaromatic compounds have been used. This notable absence can be explained, however, by the well-documented obstacles to using such heteroaromatic substrates, particularly 2-heteroaromatic compounds.

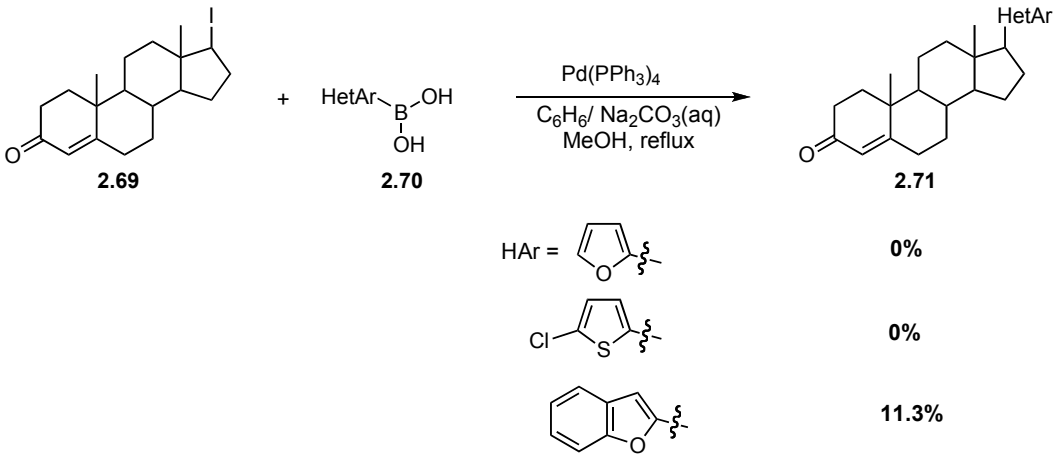
2.4.1 Protodeboronation of 2-Heteroaromatic Boronic Acids

Aryl boronic acids are the preferred aryl substrate in both the rhodium and palladium-catalyzed methods, owing in large part to their commercial availability. Unfortunately, however, aryl boronic acids are known to suffer from protodeboronation, so the aryl boronic acid is often used in large excess (up to five-fold). In the case of heteroaromatic boronic acids, the propensity for protodeboronation is much greater, with the highest rate being observed for 2-heteroarylboronic acids. This increased susceptibility to protodeboronation is due to the proximity of the heteroatom to the boron, which accelerates the rate of boron-carbon hydrolytic cleavage.[72-76] Indeed, Hayashi reported that "to the best of our knowledge, heteroaromatic groups have not been introduced enantioselectively by the rhodium-catalyzed asymmetric 1,4-addition, probably due to the instability of the corresponding boronic acids under the reaction conditions, the reactions typically being carried out in dioxane/H_2O at 100 °C."[70] In order to circumvent these problems, it was necessary to use the highly reactive catalyst $[Rh(OH)BINAP]_2$ in order to effect the conjugate addition of 3-thiopheneboronic acid at milder temperatures (Table 2.5). Hayashi did not report the addition of 2-thiopheneboronic acid to enones or enoates, presumably because that substrate will not survive the 40 °C temperature long enough to undergo transmetallation.

2-Heteroarylboronic acids have also been problematic in Pd-catalyzed Suzuki-Miyaura reactions, owing to competitive protodeboronation reactions (Scheme 2.12).[77] For example, Buchwald has reported problems with Suzuki-

Miyaura reactions between furanyl- and pyridyl boronic acids and less reactive aryl halides, such as aryl chlorides.[78]

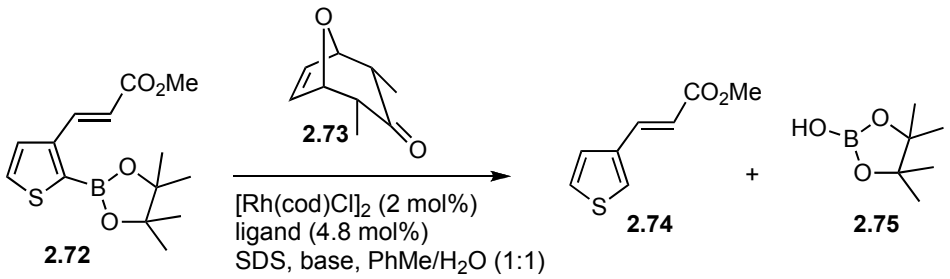
Scheme 2.12



2.4.2 Attempts to Circumvent Protodeboronation

Attempts to circumvent the instability of boronic acids have often involved the use of their more stable, boronate ester derivatives. However, even in those cases, deleterious protodeboronation reactions often occur, as exemplified by Lautens's failed attempt to achieve a successful Heck cross-coupling reaction between a stablized 2-thophenylboronate ester and a strained olefin (Scheme 2.13). Despite screening a wide variety of solvents, water ratios, and bases, the only product recovered from the reaction was protodeboronated material.[79]

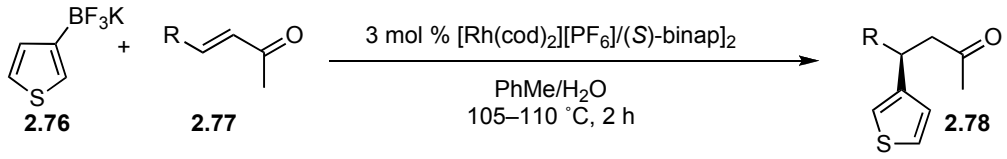
Scheme 2.13



Bases screened: Na_2CO_3, KF, CsF, $Ba(OH)_2$, NaOH, and Tl_2CO_3

Potassium trifluoroborate salts, which have also been prepared from the corresponding boronic acid by treatment with KHF_2, have exhibited slight advantages over their boronic acid counterparts, primarily because their increased stability to air and water facilitates both their preparation and storage.[60] Darses has reported the use of a variety of aryl and alkenyltrifluoroborates with a cationic Rh(I) complex to afford 1,4-addition products with high ee's.[80-82] One significant advantage that Darses found with using trifluoroborates was the ability to reduce the nucleophile equivalency to 2.0 equivalents, which is far superior to the 5.0 equivalents often necessitated with the use of arylboronic acids. Darses reported two examples utilizing 3-thiophenyltrifluoroborate (Scheme 2.14), but no other heteroaryl examples were reported.

Scheme 2.14



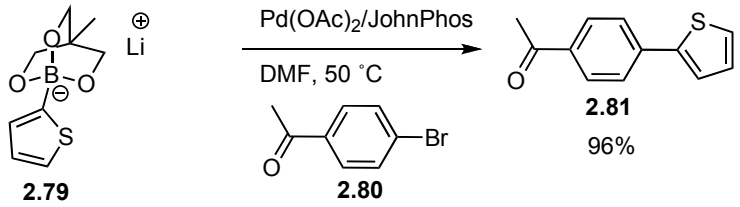
2.76 **2.77** **2.78**

R = C_5H_{11}: 84% yield; 90% ee

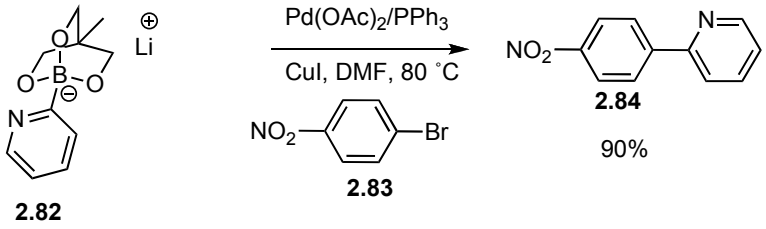
R = C_6H_{13}: 73% yield; 87% ee

One major disadvantage in using aryltrifluoroborates is that metal insertion into the carbon-boron bond can be very slow in the absence of a base, because the electronegative effect of the fluorine atoms substantially reduces the nucleophilicity of the organoboron species. In response to this problem, Miyaura and Yamamoto developed cyclic triolborates, which are also air- and water-stable but have a much greater transmetallation efficiency than aryltrifluoroborates.[83] When employing anhydrous DMF as the solvent, 2-thiophenyl- and 2-pyridyl-triolborates were effective Suzuki coupling partners (Schemes 2.15 and 2.16). It is important to note that Miyaura's conditions necessitated *aqueous* DMF for the smooth coupling of the vast majority of aryltriolborates, the exception being the 2-heteroaryltriolborates where it was crucial that *anhydrous* solvent be used in order to prevent water-catalyzed protodeboronation. As a result of the anhydrous conditions required in these cases, it was also necessary to add phosphine ligands as phosphine-free $Pd(OAc)_2$-catalyzed Suzuki couplings typically require the presence of water to promote the reduction of $Pd(OAc)_2$ to Pd(0). The addition of a copper additive in the case of pyrid-2-yltriolborate **2.82** was found to be necessary in order to achieve high yields of the biaryl product **2.84**.

Scheme 2.15

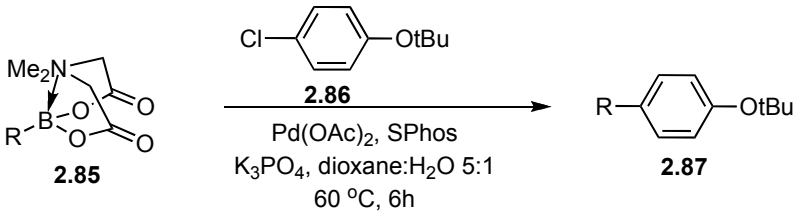


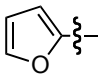
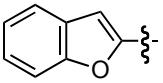
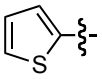
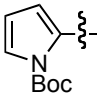
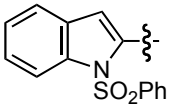
Scheme 2.16



Burke and co-workers recently developed *N*-methyliminodiacetic acid (MIDA) boronates as an alternative solution to the use of unstable 2-heteroaromatic boronic acids (Table 2.6).[84] These MIDA boronates can be hydrolyzed slowly *in situ* with the addition of K_3PO_4 at 60 ˚C, thereby slowly releasing small amounts of the reactive, but unstable boronic acids during the course of the reaction. The rate of hydrolysis increases with temperature. Using this method, Burke was able to employ 2-thiophenyl-, 2-furanyl-, 2-benzofuranyl, 2-pyrrolyl-, 2-pyridyl and 2-indolyl-MIDA boronates in a variety of coupling reactions in high yields. Although this solution is promising in the context of Pd-catalyzed couplings, the requirement of base is potentially incompatible with Rh(I)-catalyzed conjugate addition chemistry. In addition, the synthesis of some of the 2-heteroaryl MIDA boronates is low yielding, e.g. 2-pyridyl-boronates, 27%; 2-pyrrolyl-boronates, 29%, and 2-indolyl-boronates, 69%.

Table 2.6



Entry	R	Yield of **2.87** (%)
1		94
2		92
3		94
4		90
5		93

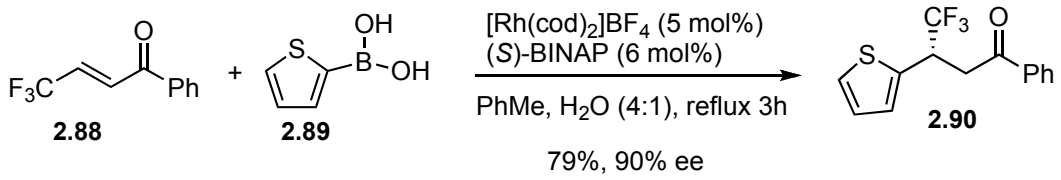
2.5 RECENT EXAMPLES OF ENANTIOSELECTIVE CONJUGATE ADDITION EMPLOYING 2-HETEROARYL COMPOUNDS

At the outset of this research there were no examples of the enantioselective conjugate addition of 2-heteroaryl compounds. However, during the course of this work and concurrent with our own research, two different reports were published illustrating the successful use of a limited range of 2-heteroaryl compounds.

The first example was reported by Ishihara and co-workers, who described one example of a Rh(I)-catalyzed enantioselective addition of 2-thiopheneboronic

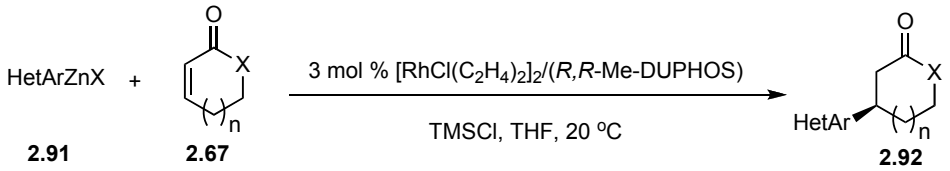
acid to a Michael acceptor (Scheme 2.17). Ishihara's reaction did not suffer from deleterious protodeboronation of **2.89**, which is somewhat surprising because the reaction was conducted under reflux in aqueous toluene.[85] However, the electronically biased nature of the electrophile was likely a contributing factor to the success of the 1,4-addition. In light of the biased acceptor used, the high temperatures employed, and the necessity for aqueous solvent, this method does not appear to be generalizable to other 2-heteroaromatic compounds and simple enones.

Scheme 2.17

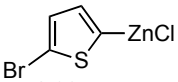
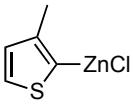
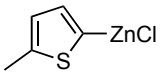
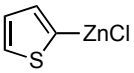
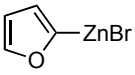


A more general method was published by Frost and coworkers in 2008.[86] In this procedure, various thiophen-2-ylzinc chlorides were employed in Rh-catalyzed enantioselective conjugate additions to cyclic enones and 5,6-dihydro-2*H*-pyran-2-one (Table 2.7, entries 1–7). The catalyst system used is derived from Me-DUPHOS and $[Rh(C_2H_4)_2Cl]_2$. 2-Cyclopenten-1-one is a poor substrate in this method, the corresponding reaction with 2-thiophenylzinc chloride proceeding in only 26% ee. Frost also reported two examples of the addition of furan-2-yl zinc bromide to 2-cylcohexen-1-one and 5,6-dihydro-2*H*-pyran-2-one, those reactions proceeding in 70 and 86% ee, respectively (Table 2.7, entries 8 and 9).

Table 2.7



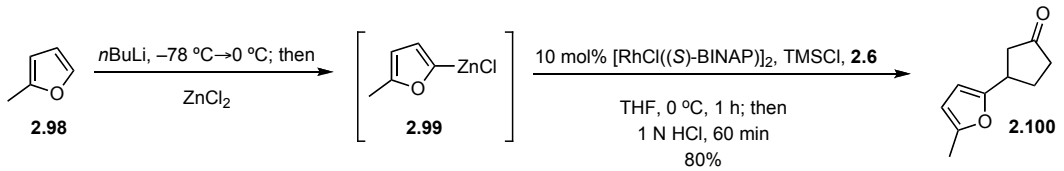
2.91 **2.67** **2.92**

Entry	HetArZnX	X	n	Yield (%)	ee (%)
1	 **2.93**	-CH_2-	1	65	64
2	 **2.94**	-CH_2-	1	91	92
3	**2.94**	O	1	76	98
4	**2.94**	O	1	94	92
5	 **2.95**	O	1	56	82
6	 **2.96**	O	1	81	92
7	**2.96**	-CH_2-	0	73	26
8	 **2.97**	-CH_2-	1	72	70
9	**2.97**	O	1	57	86

2.6 MODEL STUDIES INVOLVING FURAN-2-YL ZINC AND TITANATE REAGENTS

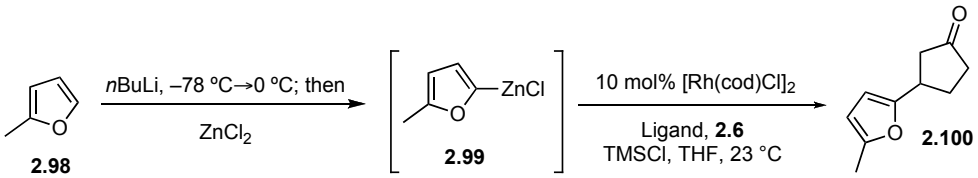
Based upon the literature precedent available at the time we initiated this research, the most relevant methodology for our purposes was clearly that developed by Hayashi. Therefore, initial trials used catalyst conditions that were identical to those reported by Hayashi. In order to avoid the problems of protodeboronation associated with 2-heteroarylboronic acids, we started with 5-methylfuran-2-ylzinc chloride (**2.99)** which was prepared from lithiation at the 5-position of 2-methylfuran and subsequent transmetallation to zinc chloride. In the event, **2.99** was added to 2-cyclopenten-1-one in the presence of [RhCl(*S*)-BINAP)]$_2$ and TMSCl to furnish the adduct **2.100** in 80% yield (Scheme 2.18).

Scheme 2.18



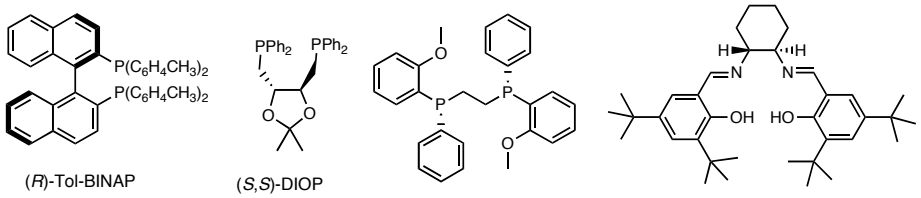
Disappointingly, however, the enantiomeric excess of the desired adduct was about 0%. In an effort to improve the enantiomeric excess, a variety of chiral ligands were screened (Table 2.8) with 5-methylfuran-2-ylzinc chloride as the model substrate. Much to our surprise, none of these ligands increased the enantiomeric excess of the adduct.

Table 2.8



entry	ligand	yield (%)	ee (%)[a,b]
1	(*S*)-BINAP	80	0
2	(*S*)-DIOP	83	0
3	(*S,S*)-DIPAMP	87	0
4	(*R,R*)-Jacobsen Ligand	75	0
5	(*R*)-Tol-BINAP	88	0

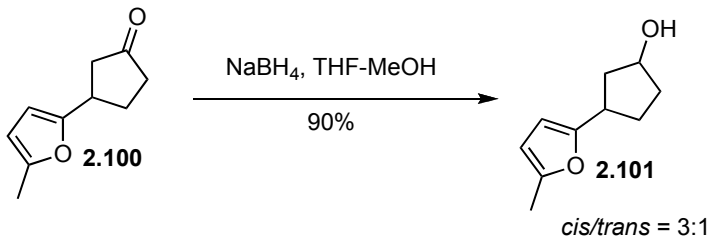
Reaction conditions: 10 mol % of $[Rh(cod)Cl]_2$, 0.75 mmol of TMSCl, ligand/Rh (1.1:1), 1.0 mmol of furan-2-ylzinc chloride, 0.5 mmol of 2-cyclopenten-1-one. [a]Determined by HPLC analysis (OD-H chiral column, 98:2 hexanes/2-propanol, 0.5 mL/min). [b] HPLC analysis was performed on the four diastereomeric alcohol derivatives of the product, formed by $NaBH_4$ reduction of **2.100**.



(*R*)-Tol-BINAP (*S,S*)-DIOP (*S,S*)-DIPAMP Jacobsen's Ligand

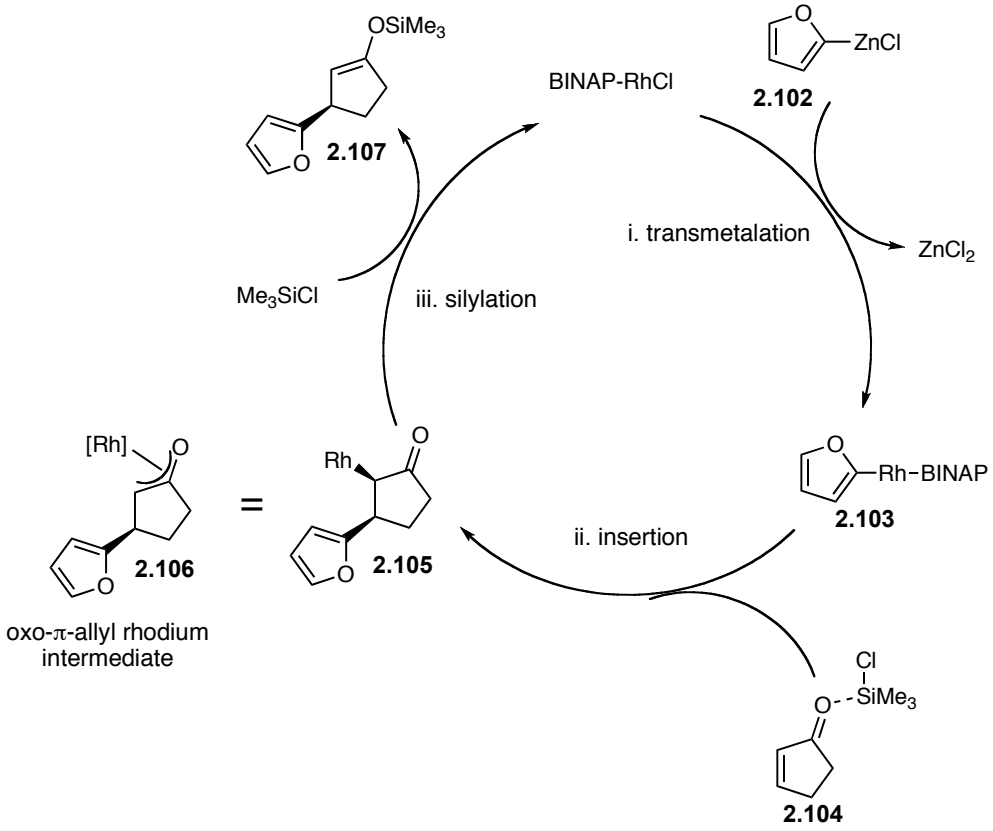
The enantiomeric excess was determined by chiral HPLC analysis of the the enantioenriched substrate and comparison to a racemic standard. The 1,4-adduct **2.100** could not be separated via chiral HPLC, and therefore the ee was determined by evaluation of the derivative **2.101**, formed from $NaBH_4$ reduction of the 1,4-adduct (Scheme 2.19). The four diastereomers could be separated by chiral HPLC and the enantiomeric pairs could be designated on the basis of comparison to the *cis*/*trans* ratio, which was determined by ^1H NMR integration.

Scheme 2.19



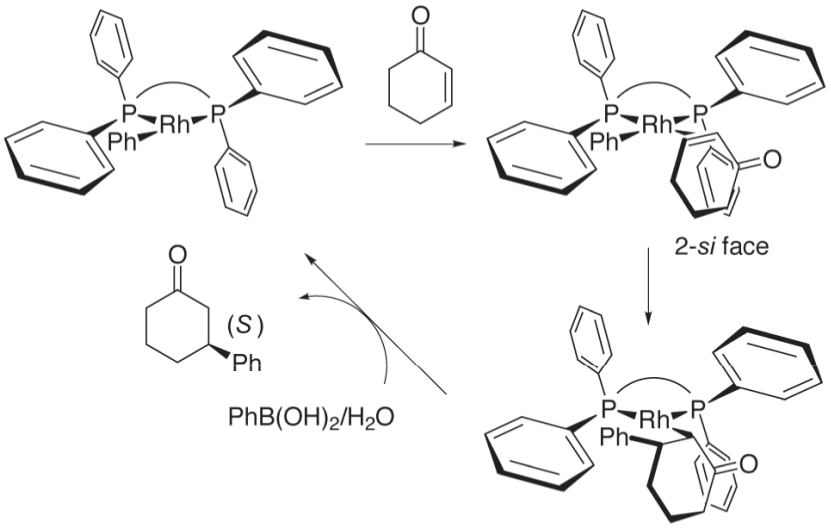
In considering the reaction, we envisioned the catalytic cycle to be similar to that proposed by Hayashi (Figure 2.5). The first step in the cycle is transmetallation of the furan-2-ylzinc species **2.102** to rhodium, producing the chiral furan-2-ylrhodium species **2.103**. TMSCl activates the enone towards addition and in the second step, an enantiodiscriminating olefin insertion takes place, leading to rhodium enolate **2.106**. The active rhodium species is regenerated by the assistance of TMSCl which silylates the enolate oxygen of **2.106**, along with concomitant transfer of a chlorine atom to rhodium.

Figure 2.5



In order to achieve enantiodiscrimination in the insertion step, one face of the olefin must be selectively accessible to the nucleophile (Figure 2.6).[87] Before our ligand screening, we had presumed that our absence of ee resulted from poor olefin discrimination in this step of the cycle. However, in light of the fact that a variety of ligands did not alter the ee at all, we began to suspect that the problem would not be solved by exhaustive ligand screening.

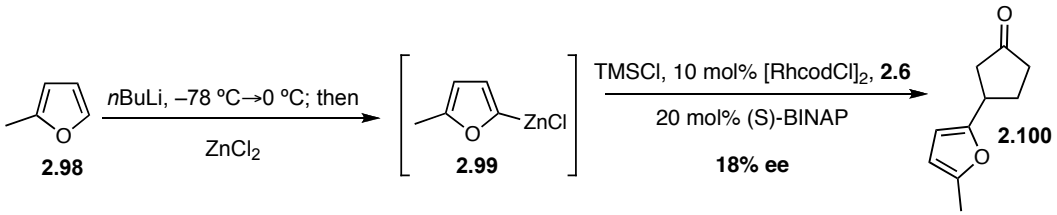
Figure 2.6



2.6.1 Background Reaction

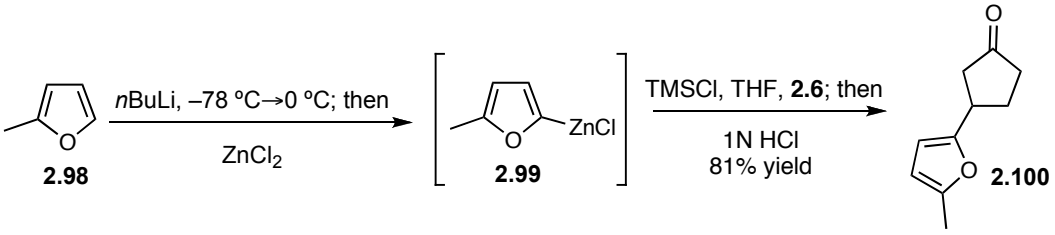
In an effort to probe the reaction further, a fortuitous control experiment was performed in which the influence of the rate of addition of the nucleophile was examined. Interestingly, slow addition (2 mmol/hr) of the nucleophile **2.99** to 2-cylopenten-1-one resulted in a modest ee of 18% (Scheme 2.20). This was the first observation of modest enantiomeric excess using these reaction conditions.

Scheme 2.20



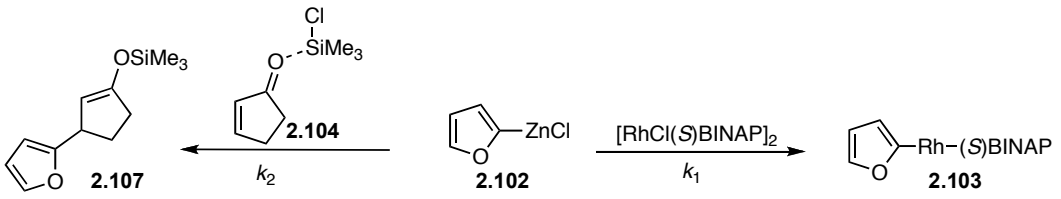
The influence of the rate of addition of the nucleophile upon the enantiomeric excess of the product is consistent with the presence of a competing background reaction. In order to investigate that possibility, a second control reaction was performed in the absence of catalyst. In the event, the 1,4-addition product **2.100** was obtained in 81% yield, confirming that a background reaction was likely occurring (Scheme 2.21). This result strongly suggested that the low enantiomeric excess resulted from an incomplete transmetallation step in the catalytic cycle.

Scheme 2.21



With the presence of a background reaction, there are presumably two competing pathways (Equation 2.1). If the transmetallation of the furylzinc chloride to the rhodium is slow compared to the uncatalyzed addition of furylzinc chloride to 2-cyclopenten-1-one, enantioselectivity will be diminished. The magnitude of diminishment will be relative to the difference in the competing rates k_1 and k_2.

Equation 2.1



If $k_1 < k_2$, then diminished ee will result

The rate of addition of the nucleophile to the reaction will further bias this competition. If the nucleophile is added via a fast addition, considering there is substoichiometric catalyst present, there will be a much greater concentration of **2.102** in solution relative to the catalyst. Without any catalyst to react with, the excess nucleophile cannot undergo transmetallation and will proceed along the competing pathway to furnish racemic material. Slowing the addition of the nucleophile has the effect of lowering the concentration of the nucleophile, relative to the catalyst, and thereby decreasing the bias towards the undesired competing pathway.

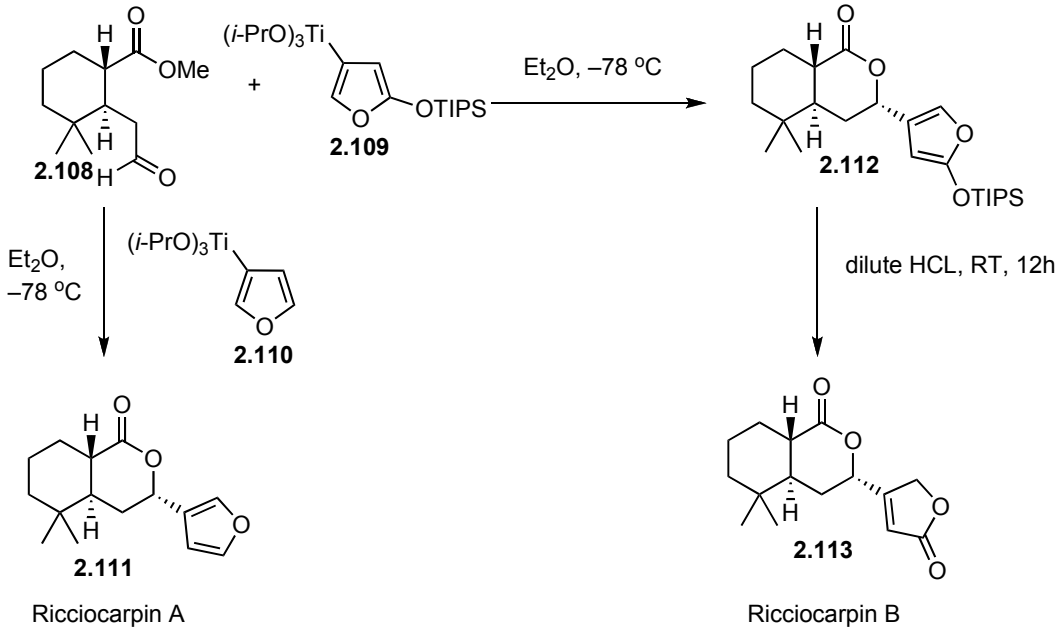
There is no literature precedent for the conjugate addition of a simple furan-2-ylzinc chloride to an enone, which is why this background reaction was not anticipated. In fact, much more complex furan species have been employed to accomplish the same transformation, such as Lipshutz's higher order cyanocuprates and Knochel's mixed diorganozincs.[37, 38] Furan-2-ylzinc chloride is not only much simpler to synthesize, but is also more atom economical. In comparison, Lipshutz's method only transfers one of two furan ligands from copper and Knochel's method requires a sacrificial dummy ligand on zinc.

2.6.2 Employing Furan-2-yl Titanates

Although employing slow addition did result in an improved ee, it was not high enough to be synthetically useful. Therefore, efforts were focused on finding a different organometallic species that did not suffer from a competing background reaction. Towards that end, we investigated the use of 2-heteroaryltitanium reagents.

While there is no literature precedent regarding the use heteroaryltitanium species in Michael reactions, furan-3-yl titanates have been used infrequently in 1,2-additions to aldehydes. Sibi employed a furan-3-yltitanium reagent, in a diastereoselective 1,2-addition to an aldehyde in his synthesis of Ricciocarpins A and B (Scheme 2.22).[88]

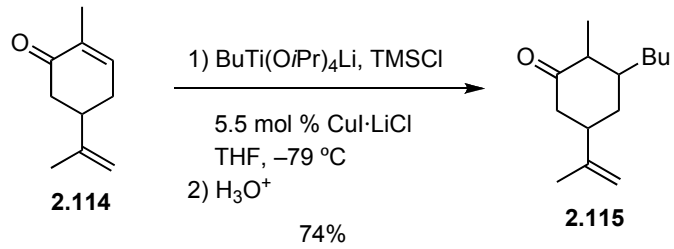
Scheme 2.22



A similar 1,2-addition was employed by Boukouvalas in his synthesis of (+)-Zerumin B,[89] as well as in his synthesis of (+)-Dysidiolide.[90] Other than these examples, however, the use of heteroaryltitanium reagents in organic synthesis has been relatively unexplored.[91]

In the area of alkyltitanium reagents, Lipshutz has reported the conjugate addition of butyltitanates in the presence of TMSCl and catalytic CuI•LiCl (Scheme 2.23).[92, 93] No asymmetric variants of this reaction have been reported to date.

Scheme 2.23



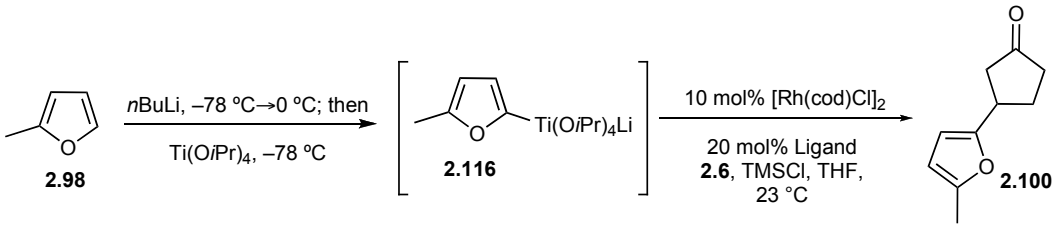
2.114 **2.115**

In contrast to the dearth of reactions involving heteroaryltitanium reagents, aryltitianium reagents have been used more frequently. As mentioned above, Hayashi has used aryltitanium triisopropoxides [ArTi(OPr-*i*)$_3$] and aryltitanates [ArTi(OPr-*i*)$_4$]Li in Rh-catalyzed 1,4-additions (Table 2.4). While both organometallic reagents worked well, the "ate" species furnished higher yields with 2-cyclopenten-1-one than did the neutral titanium reagent.

With no literature precedent to indicate whether furan-2-yl titanates would participate in uncatalyzed conjugate additions, like their zinc counterparts, we attempted the reaction using 5-methylfuran-2-yltitanate with our standard conditions. To our delight, the conjugate addition adduct was obtained in 85%

yield and 84% ee (Table 2.9, entry 1). By screening a variety of ligands, this ee was improved to 90% with the use of (*R*)-Tol-BINAP (Table 2.9, entry 5).

Table 2.9

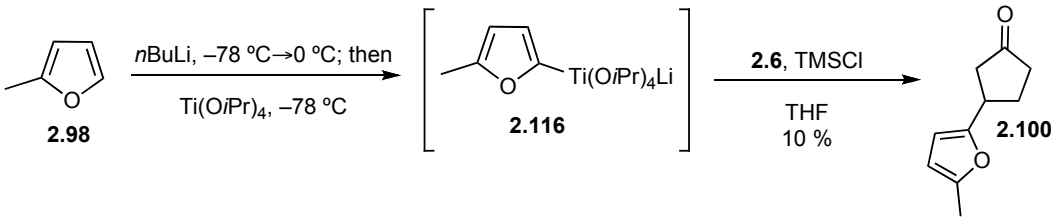


entry	ligand	yield (%)	ee (%)
1	(*S*)-BINAP	85	84
2	(*S*)-DIOP	5	n.d.
3	(*S,S*)-DIPAMP	10	n.d.
4	(*R,R*)-Jacobsen Ligand	5	n.d.
5	(*R*)-Tol-BINAP	84	90

n.d. = not determined

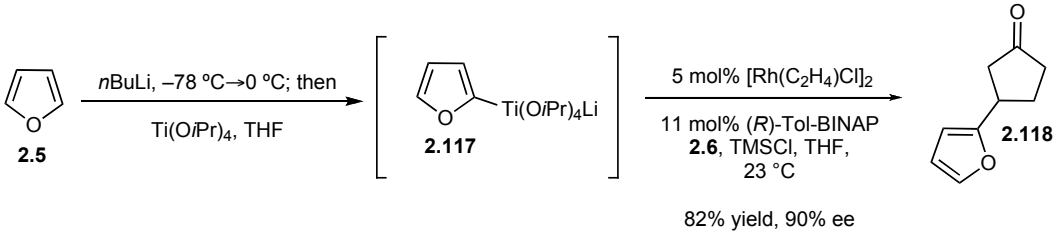
Although high ee had been achieved with the titanate, a control experiment was performed to test for the presence of any background reactions. Subjection of furan-2-yl titanate **2.116** to the reaction conditions, in the absence of catalyst, furnished the 1,4-addition product in 10% yield, indicating that a minor background reaction was present (Scheme 2.24). Considering that a 90% ee had been achieved using titanate **2.116**, it is plausible that the ee for the Rh-catalyzed pathway may indeed be closer to 100%.

Scheme 2.24

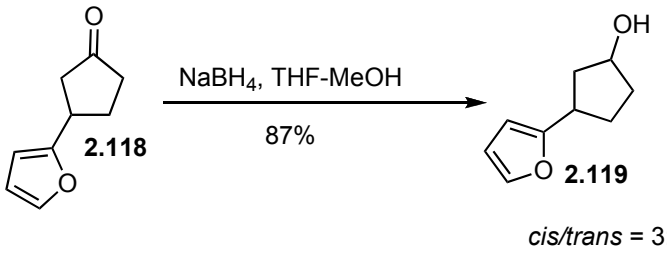


Although we were pleased with the ee of the reaction, the catalyst loading was still rather high. However, we found that changing the rhodium pre-catalyst to $[Rh(C_2H_4)_2Cl]_2$ enabled the catalyst loading to be reduced by half without compromising the yield or enantioselectivity (Scheme 2.25). Enantiomeric excess was determined by HPLC analysis of the derivative **2.119**, which was formed by $NaBH_4$ reduction of **2.118** (Scheme 2.26).

Scheme 2.25



Scheme 2.26



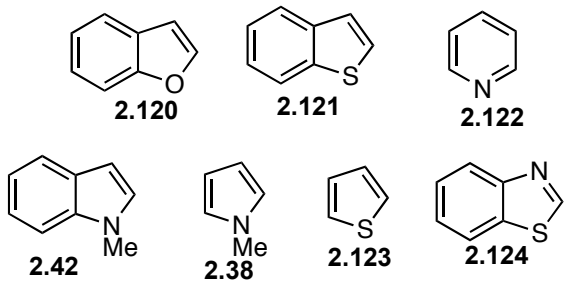
To date, this result represents the only example of an enantioselective addition of a furan-2-yl nucleophile to 2-cyclopenten-1-one. At the time it was

discovered, it was also the first example of an enantioselective 1,4-addition of a 2-heteroaromatic nucleophile to a Michael acceptor. Additional noteworthy attributes of the reaction include the fact that it is performed in anhydrous solvent and that it is not necessary to perform this chemistry in a glovebox as the active catalyst can be generated *in situ* using standard Schlenk technique.

2.7 EXTENSION TO OTHER 2-HETEROAROMATIC NUCLEOPHILES AND MICHAEL ACCEPTORS

Due to the lack of literature precedent for adding 2-heteroarylnucleophiles to Michael acceptors, we thought it would be valuable to generalize our reaction to include other heteroaromatic substrates and Michael acceptors. A variety of heteroaromatic compounds were identified as desirable nucleophiles (Figure 2.7). Of these compounds, only thiophene had been added to an enone enantioselectively. It was postulated that the titanate derivatives of all of these compounds could be made by facile direct lithiation at the 2-position and subsequent transmetallation to the corresponding heteroaryl titanium reagent with titanium tetraisopropoxide.

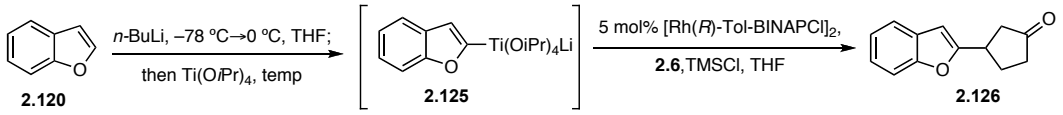
Figure 2.7



2.7.1 Studies with Benzofuran

Initial attempts to add the benzofuran-2-yl titanate **2.125** to 2-cyclopenten-1-one using the same reaction conditions previously established for furan failed to furnish any of the desired 1,4-adduct **2.126**. However, subsequent screening of conditions led to the discovery that the temperature at which the benzofuranyltitanate **2.125** is prepared is of critical importance, with lower temperatures facilitating higher yields (Table 2.10).

Table 2.10



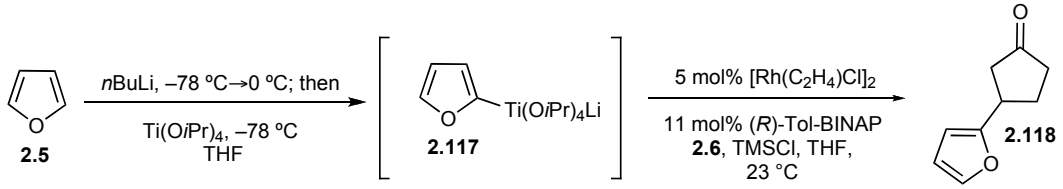
Entry	Temp	Yield (%)	ee (%)
1	–78 ˚C	37	90
2	–40 ˚C	8	n.d.
3	–20 ˚C	8	n.d.
4	0 ˚C	1	n.d.
5	RT	0	n.d.

n.d. = not determined

This temperature sensitivity was surprising as it had not been observed previously with furan. Subsequent experiments with the furan-2-yltitanate **2.117**

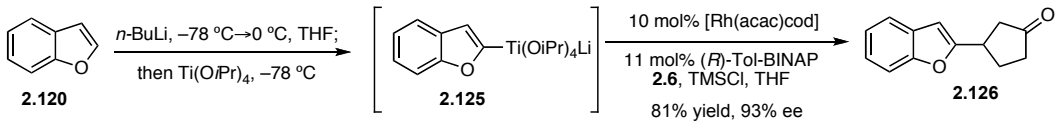
indicated that slightly higher yields could be obtained with furan by also preparing its titanate complex at –78 ˚C (Scheme 2.27). In light of these findings, the titanate complexes of all subsequent 2-heteroaryl substrates were also prepared at –78 ˚C.

Scheme 2.27



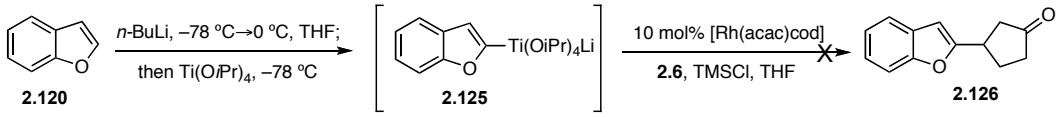
In addition to temperature sensitivity, further optimization with benzofuran revealed that the choice of rhodium pre-catalyst dramatically affects product yields. A dramatic increase in yield was observed by simply using [Rh(acac)cod] as the pre-catalyst rather than $[Rh(C_2H_4)_2Cl]_2$ (Scheme 2.28). Hayashi has reported that the acetylacetonato (acac) ligand retards the transmetallation step because of the high stability of the rhodium-acac moiety,[94] which was a disadvantage in his method. However, in the context of our experiments with benzofuran, the presence of an acac ligand was clearly advantageous.

Scheme 2.28



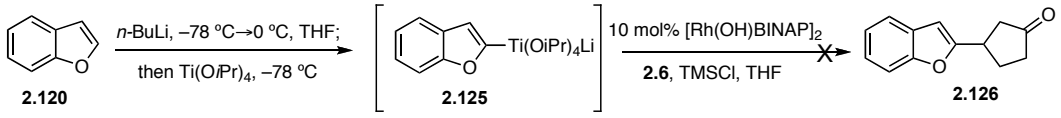
As it is known that [Rh(acac)cod] is a very active conjugate addition catalyst by itself,[95] a control reaction was performed in the absence of chiral ligand (Scheme 2.29). None of the desired product was obtained, indicating that [Rh(acac)cod] is *not* an active catalyst for this transformation.

Scheme 2.29



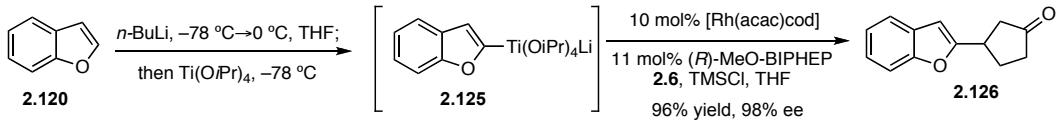
Since Hayashi reported $[Rh(OH)BINAP]_2$ to be an extremely active catalyst for the conjugate addition of 3-thiopheneboronic acid, this catalyst was also tested in our optimization studies. $[Rh(OH)BINAP]_2$ is known to be extremely air-sensitive and is typically made and handled in a glovebox. As it is undesirable to develop a method that requires a glovebox, the *in situ* preparation of $[Rh(OH)BINAP]_2$ was attempted in a Schlenk flask. During the preparation the catalyst solution turned black, which is a possible indication of catalyst decomposition. Nonetheless, this black solution was used immediately in the conjugate addition reaction, but failed to produce any of the desired product.

Scheme 2.30



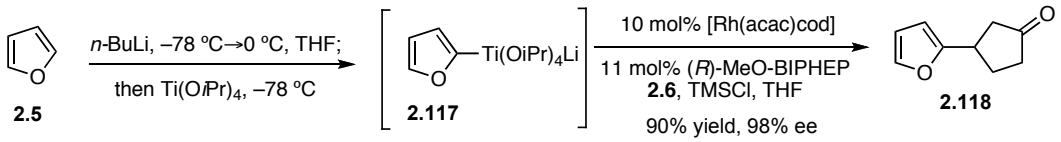
Finally, additional ligand screening led to the identification of (*R*)-MeO-BIPHEP as the optimal ligand of choice. In the presence of [Rh(acac)(*R*)-MeO-BIPHEP], the desired adduct was isolated in 96% yield and 98% ee (Scheme 2.31).

Scheme 2.31



Gratifyingly, when these newly optimized catalyst conditions were applied to the addition of furan-2-yl titanate **2.116** to 2-cyclopenten-1-one, a similar improvement in ee was also observed (Scheme 2.32). Having optimized the reaction conditions for benzofuran and furan, our attention then was directed to applying these optimized conditions to our other target heterocycles (Figure 2.7).

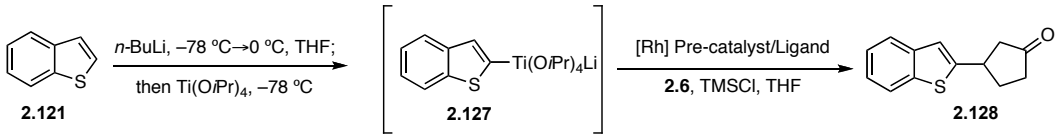
Scheme 2.32



2.7.2 Studies with Benzothiophene

Optimization studies with benzothiophen-2-yl titanate showed a similar dependence upon the choice of rhodium pre-catalyst, as was seen with benzofuran. In all cases, [Rh(acac)cod] furnished the best yields (Table 2.11). Additionally, (*R*)-MeO-BIPHEP proved to be a superior ligand to (*R*)-Tol-BINAP, in regard to both yield and enantiomeric excess.

Table 2.11



2.121 2.127 2.128

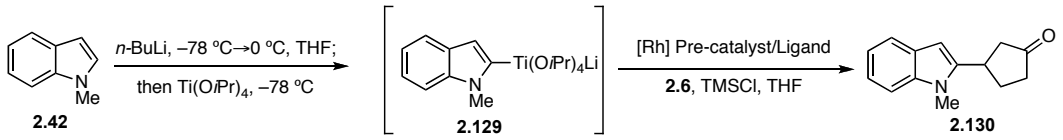
Entry	Pre-catalyst/Ligand	Yield (%)	ee(%)
1	5 mol% $[Rh(C_2H_4)_2Cl]_2$/(*R*)-Tol-BINAP	0	n.d.
2	10 mol% [Rh(cod)acac]/(*R*)-Tol-BINAP	36	90
3	10 mol% [Rh(cod)acac]/(*R*)-MeO-BIPHEP	69	95

n.d. = not determined

2.7.3 Studies with Indole

In agreement with benzothiophene, benzofuran, and furan, [Rh(acac)(R)-MeO-BIPHEP] was a superior catalyst to $[Rh(C_2H_4)_2$(*R*)-Tol-BINAP] in the addition of *N*-methylindol-2-yl titanate **2.129** to 2-cyclopenten-1-one (Scheme 2.33). Although the yield was lower than the other heterocycles surveyed, the enantiomeric excess was gratifyingly high.

Scheme 2.33



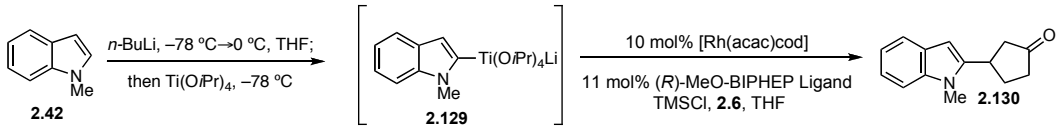
2.42 2.129 2.130

Pre-catalyst/Ligand	Yield (%)	ee(%)
5 mol% $[Rh(C_2H_4)_2Cl]_2$/(*R*)-Tol-BINAP	12	n.d.
10 mol% [Rh(cod)acac]/(*R*)-MeO-BIPHEP	47	90

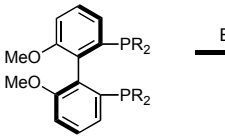
(n.d. = not determined)

In an effort to increase the yield of the indole addition, a variety of ligands from the (*R*)-MeO-BIPHEP family were screened (Table 2.12). Unfortunately, none of these ligands afforded a higher yield than that observed with (*R*)-MeO-BIPHEP.

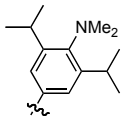
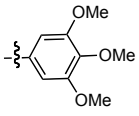
Table 2.12



2.42 2.129 2.130

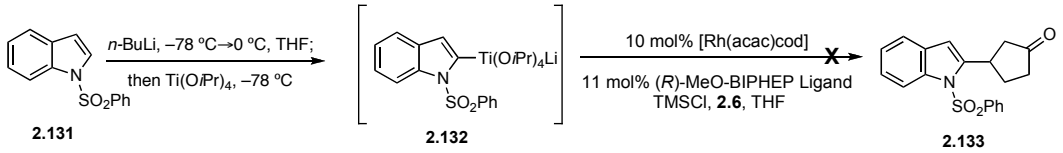


(*R*)-MeO-BIPHEP Ligand

Entry	BIPHEP Ligands R =	Yield (%)
1		0
2		14
3		33
4		42

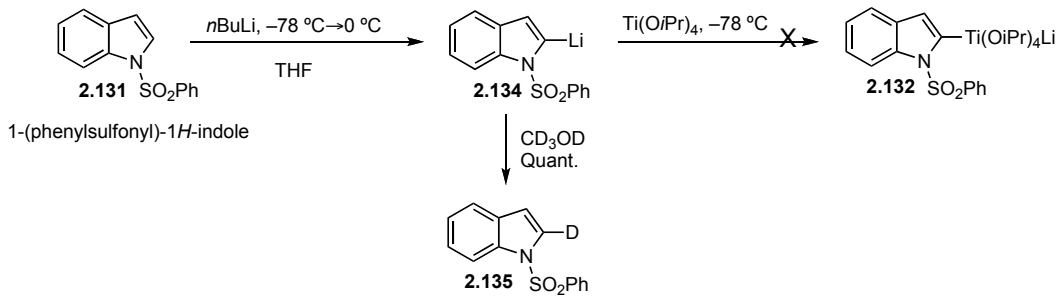
One interesting observation in the case of the indole nucleophile was that the nature of the group on indole nitrogen was critical to the outcome of the 1,4-addition. For example, when the titanate of 1-(phenylsulfonyl)-1*H*-indole was used under the established conditions, it failed to yield any of the desired adduct (Scheme 2.34).

Scheme 2.34



The explanation for this result may be found in the preparation of titanate species **2.132**. Titration of **2.132** with iodine indicated that the titanate species may not have been formed. In order to establish which step of the titanate preparation was problematic, a deuterium quench was performed on the lithiated intermediate **2.134** (Scheme 2.35). Quantitative deuterium incorporation was observed, indicating that lithiation had been quantitative, and thus the problem must lie in the transmetallation from lithium to titanium.

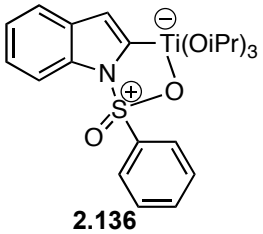
Scheme 2.35



Without any literature precedent about indol-2-yl titanates to inform our research, it was difficult to identify possible explanations for this obstacle. The fact that the solution containing the supposed titanate species **2.132** could not be titrated with iodine is inconsistent with the possibility that only the lithiated indole **2.134** and unreacted titanium tetraisopropoxide were in solution. Had that been the case, the lithiated species **2.134** would have reacted with iodine, giving the false impression that the transmetallation had succeeded. In fact, that is a drawback in using iodine for the titration of titanates, but we are unaware of a titration method that can distinguish between a titanium and lithium species.

One possible explanation may be that transmetallation did occur, but due to the oxaphilic nature of titanium, an unreactive complex, such as **2.136**, may have formed (Figure 2.8). Without isolating a crystal of such a complex, however, this is a simply a hypothetical guess.

Figure 2.8



2.136

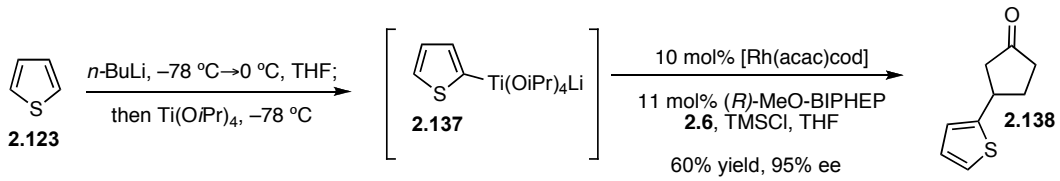
Possible unreactive complex

2.7.4 Studies with Thiophene

Using our optimized conditions, thiophen-2-yl titanate **2.137** was added to 2-cyclopenten-1-one in moderate yield and excellent enantiomeric excess (Scheme 2.36). In view of the poor enantioselectivity reported by Frost for the

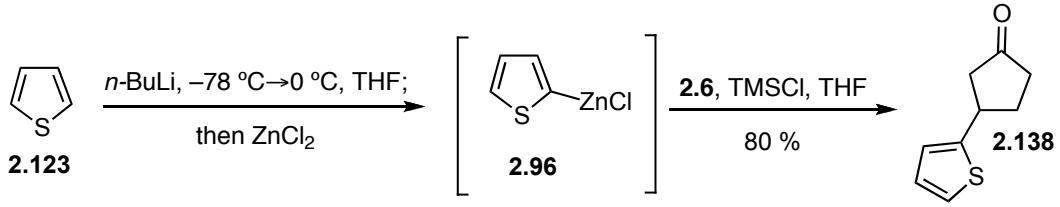
addition of thiophen-2-ylzinc reagents to 2-cyclopenten-1-one, e.g. 26%, it is noteworthy that the corresponding titanate furnished such a high ee.

Scheme 2.36



Frost's observed ee is consistent with a background reaction like what we had observed in the case of furan. To investigate this possibility, a control reaction was performed with thiophen-2-ylzinc chloride in the absence of catalyst. In the event, the 1,4-adduct was obtained in 80% yield (Scheme 2.37). This result emphasizes the critical importance of the metal in furnishing adequate ee.

Scheme 2.37

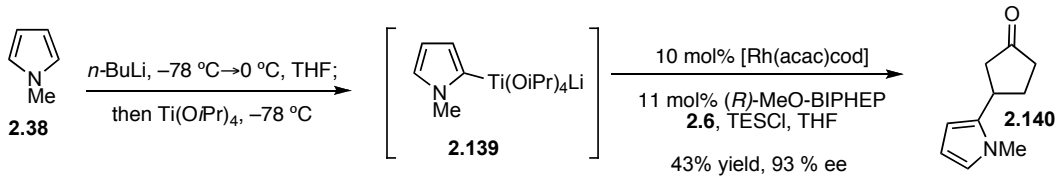


2.7.5 Studies with N-Methylpyrrole

Of all the heterocycles examined, N-methylpyrrol-2-yl titanate **2.139** was the most difficult substrate to work with due to the propensity of the 1,4-addition product to polymerize under the acidic conditions of the workup. A number of alternative workup conditions were screened in an effort to hydrolyze the silyl enol ether without inducing polymerization, including the use of fluoride sources, hydroxide, and other basic conditions, but none were an improvement upon the

standard workup conditions using dilute aqueous HCl. One change that did slightly improve the outcome with this substrate was the use of TESCl in place of TMSCl as the Lewis acid. Ultimately, the 1,4-adduct was achieved in 43% yield and 93% ee (Scheme 2.38).

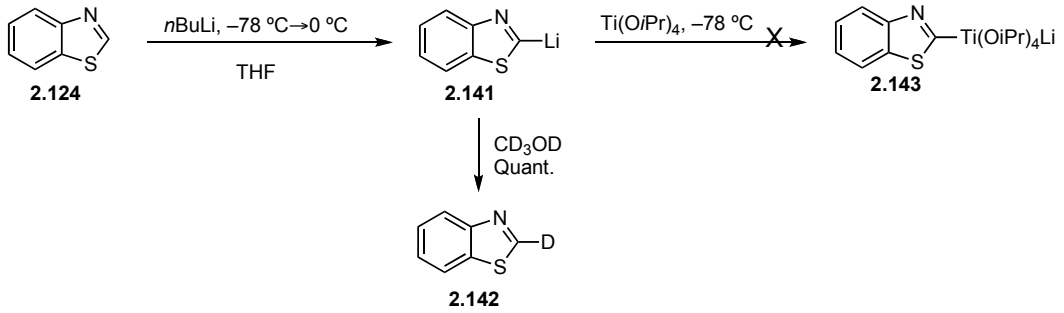
Scheme 2.38



2.7.6 Studies with Benzothiazole, Pyridine, and N-methyl-imidazole

Preliminary studies with benzothiazole, pyridine, and N-methyl-imidazole did not yield promising results. In all three cases, the formation of the titanate was problematic. Similar to what was seen in the case of 1-(phenylsulfonyl)-1*H*-indole, deuterium quenching experiments with benzothiazole (Scheme 2.39) indicated that lithiation was quantitative, but titration with iodine indicated that a reactive titanate may not have been formed. In all cases the prepared solution of titanate was carried forward through the reaction in the chance that the iodine titration was not reliable. However, in all of those cases, no product was obtained and only starting material was recovered. Similar problems were encountered with both pyridine and N-methylimidazole.

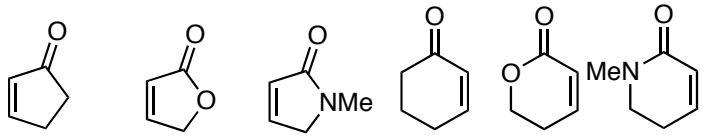
Scheme 2.39



2.7.7 Expanding the Scope of the Michael Acceptor

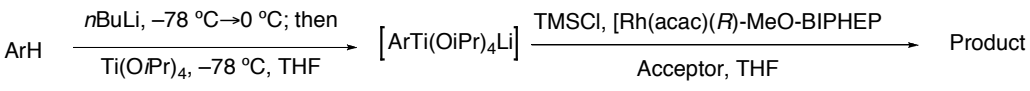
In addition to testing a variety of heteroaromatic nucleophiles, Michael acceptors other than 2-cyclopenten-1-one were investigated. The α,β-unsaturated compounds of interest include five- and six-membered enones, unsaturated lactams and lactones (Figure 2.9).

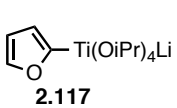
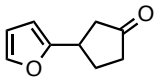
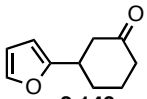
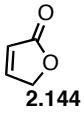
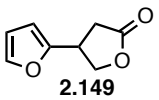
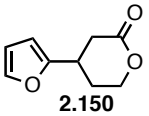
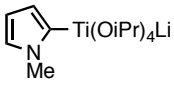
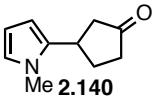
Figure 2.9



Furan and was added to both enones and unsaturated lactones efficiently, the reactions of enones typically furnished higher yields of adducts than enoates (Table 2.13). In contrast, N-methylpyrrole gave unsatisfactory yields, ca. 20-30%, with lactones. The best examples with furan and N-methylpyrrole titanates are summarized in Table 2.13.[96]

Table 2.13

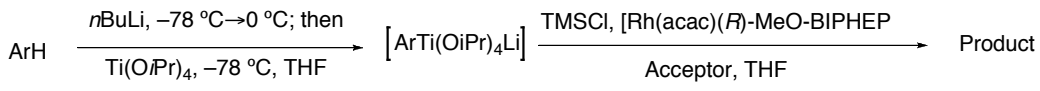


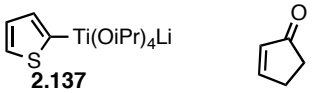
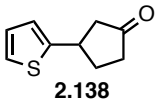
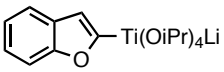
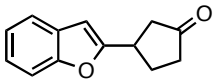
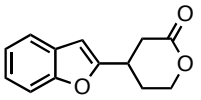
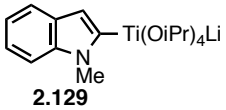
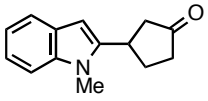
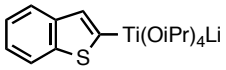
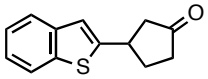
entry	$ArTi(OiPr)_4Li$	acceptor	product	yield (%)[b]	ee (%)[c]
1	 **2.117**	 **2.6**	 **2.118**	90	98[d]
2	**2.117**	 **2.21**	 **2.148**	60	94[d]
3	**2.117**	 **2.144**	 **2.149**	60	>98
4	**2.117**	 **2.146**	 **2.150**	42	97
5	 **2.139**	**2.6**	 **2.140**	43	93

[a]**Reaction conditions**: 10 mol % [Rh], Rh:L (1:1.1), [Rh] = [Rh(cod)acac]; L = (*R*)-MeO-BIPHEP, 0.45 mmol TMSCl, 0.30 mmol Michael acceptor, 0.6 mmol 2-heteroaryl titanate, THF (–78 ºC to RT). [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis (OD-H or AD chiral column). [d]HPLC analysis was performed on the four diastereomeric alcohol derivatives of the product, formed by $NaBH_4$ reduction of product.

Thiophene was not explored with other acceptors as Frost had already reported similar examples. Benzofuran-2-yl titanate added efficiently to lactone **2.146** (Table 2.14, entry 3) in good yield and excellent ee. The best examples with benzofuran, thiophene, benzothiophene, and N-methylindole titanates are summarized in Table 2.14.[96]

Table 2.14



entry	$ArTi(OiPr)_4Li$	acceptor	product	yield (%)[b]	ee (%)[c]
1	 **2.137**	**2.6**	 **2.138**	60	95[d]
2	 **2.125**	**2.6**	 **2.126**	96	>98
3	**2.125**	 **2.146**	 **2.151**	70	>98
4	 **2.129**	**2.6**	 **2.130**	47	90
5	 **2.127**	**2.6**	 **2.128**	69	95

[a]**Reaction conditions**: 10 mol % [Rh], Rh:L (1:1.1), [Rh] = [Rh(cod)acac]; L = (*R*)-MeO-BIPHEP, 0.45 mmol TMSCl, 0.30 mmol Michael acceptor, 0.6 mmol 2-heteroaryl titanate, THF (–78 ºC to RT). [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis (OD-H or AD chiral column). [d]HPLC analysis was performed on the four diastereomeric alcohol derivatives of the product, formed by $NaBH_4$ reduction of product.

2.7.8 Revisiting Zinc Reagents

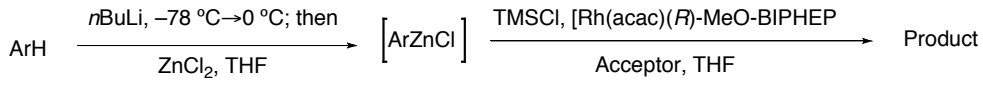
During the course of these studies, we observed that the yields of the additions of 2-heteroaryl titanates to α,β-unsaturated carbonyl compounds were

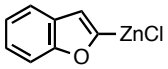
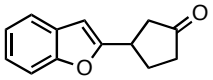
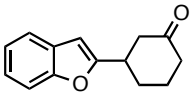
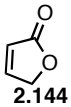
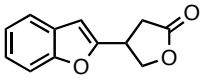
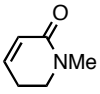
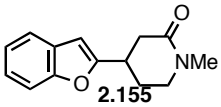
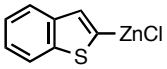
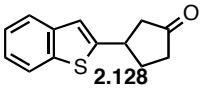
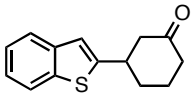
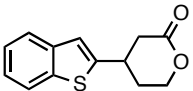
not satisfactory in some cases, even though the enantioselectivities in these reactions were consistently high. Although we had established that both thiophen-2-yl- and furan-2-yl zinc chloride added readily to 2-cyclopenten-1-one in the absence of a transition metal catalyst, it was unknown whether similar background reactions would be problematic with other 2-heteroarylzinc chlorides. As the zinc reagents are typically more stable at room temperature than the titanates, we thought that they might furnish higher yields in some cases.

Therefore, a variety of 2-heteroarylzinc chlorides were prepared and used in those cases where the titanates did not furnish sufficient product yields. A screening of pre-catalysts and chiral ligands (*e.g.,* (*R*)-Tol-BINAP, Josiphos, Walphos, and Carreira's diene) with benzofuran-2-yl zinc chloride **2.152** identified the catalyst system derived from [Rh(COD)acac] and (*R*)-MeO-BIPHEP to be optimal, in agreement with our observations from the titanate system. In a model reaction, the enantioselective addition of benzofuran-2-yl zinc chloride **2.152** to 2-cyclopenten-1-one proceeded in 91% yield and 91% ee (Table 2.15, entry 1).

Encouraged by this result, we extended this reaction to other cyclic enones and unsaturated lactones and lactams, and these conjugate additions also proceeded in good yield and excellent ee's (Table 2.15, entries 2–4). Similarly, benzothiophen-2-yl zinc chloride **2.152** added to several Michael acceptors in ≥98% ee and moderate to excellent yield (Table 2.15, entries 5–7).[96] Preliminary experiments with the addition of N-methylindolezinc chloride to 2-cyclopenten-1-one resulted in better yields than the titanate, but unsatisfactory ee.

Table 2.15



entry	ArZnCl	acceptor	product	yield (%)[b]	ee (%)[c]
1	 **2.152**	 **2.6**	 **2.126**	91	91
2	**2.152**	 **2.21**	 **2.153**	93	90
3	**2.512**	 **2.144**	 **2.154**	64	98
4[a]	**2.152**	 **2.147**	 **2.155**	62	91
5[a]	 **2.156**	**2.6**	 **2.128**	75	98
6[a]	**2.156**	**2.21**	 **2.157**	92	>98
7[a]	**2.156**	 **2.146**	 **2.158**	47	>98

Reaction conditions: 10 mol % [Rh], Rh:L (1:1.1), [Rh] = [Rh(cod)acac]; L = (*R*)-MeO-BIPHEP, 0.45 mmol TMSCl, 0.30 mmol Michael acceptor, 0.6 mmol 2-heteroaryl titanate, THF (–78 ºC to RT). [a]Reactions performed by Lily Abbott. [b]Isolated yield after flash chromatography. [c]Determined by HPLC analysis (OD-H or AD chiral column).

2.8 SUMMARY AND CONCLUSIONS

A useful methodology has been developed for the enantioselective conjugate addition of 2-heteroaryl nucleophiles to a variety of Michael acceptors, including enones, unsaturated lactones and lactams. By employing 2-heteroaryl titanium and zinc reagents, problems associated with protodeboronation of the corresponding boronic acids can be avoided entirely. We found that the nature of the organometallic reagent can have a dramatic effect on ee. In many cases the titanate reagents afforded higher ee's than their zinc counterparts, particularly in the case of furan, thiophene, and N-methylindole. However, in other cases, reactions involving zinc reagents proceeded in higher yields.

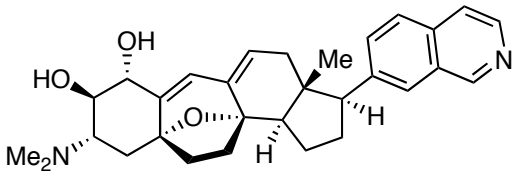
Additional attributes of the methodology include its practical nature, as the active catalyst does not require the use of a glovebox, and the use of anhydrous solvent, which allows for the possibility of isolation of silyl enol ether intermediates. The application of this method to the Martin Group's synthesis of cortistatin A has been successful and investigations into other applications of this methodology are ongoing.

Chapter 3: Studies Towards the Total Synthesis of Cortistatin A

3.1 INTRODUCTION

Cortistatin A (**2.1**) is a novel steroidal alkaloid that was isolated from the marine sponge *Corticium simplex* in 2006 by Kobayashi and coworkers (Figure 3.1).[97] Owing to its unique structure and impressive biological activity, cortistatin A has generated great interest from the synthetic community. In fact, in the short time since its isolation, 13 synthetic approaches to cortistatin A have been published, including total, partial, and formal syntheses.

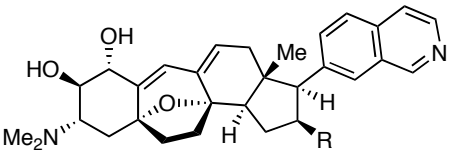
Figure 3.1



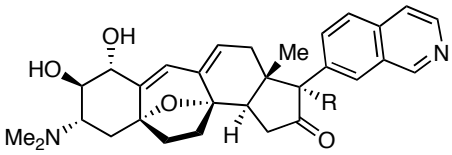
2.1
Cortistatin A

In 2007, Kobayashi isolated several additional members of the cortistatin family (Figure 3.2).[98, 99] Of these, cortistatin J exhibits the most promising biological properties, and as a result, several synthetic approaches toward this natural product have been published as well.

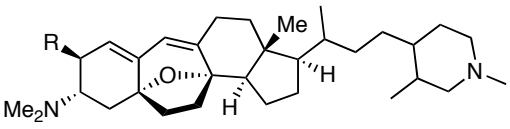
Figure 3.2



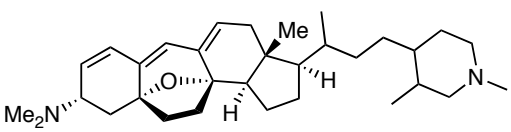
cortistatin A: R = H, **2.1**
cortistatin B: R = OH, **3.1**



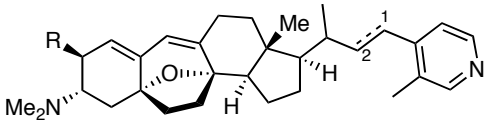
cortistatin C: R = H, **3.2**
cortistatin D: R = OH, **3.3**



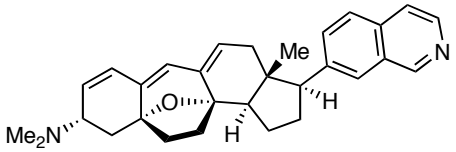
cortistatin E, **3.4**



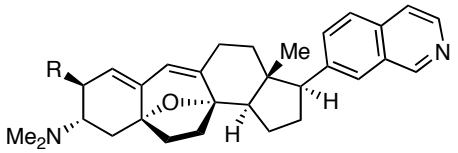
cortistatin F, **3.5**



cortistatin G: C1-C2, saturated, **3.6**
cortistatin H: C1-C2, unsaturated, **3.7**



cortistatin
J, **3.8**



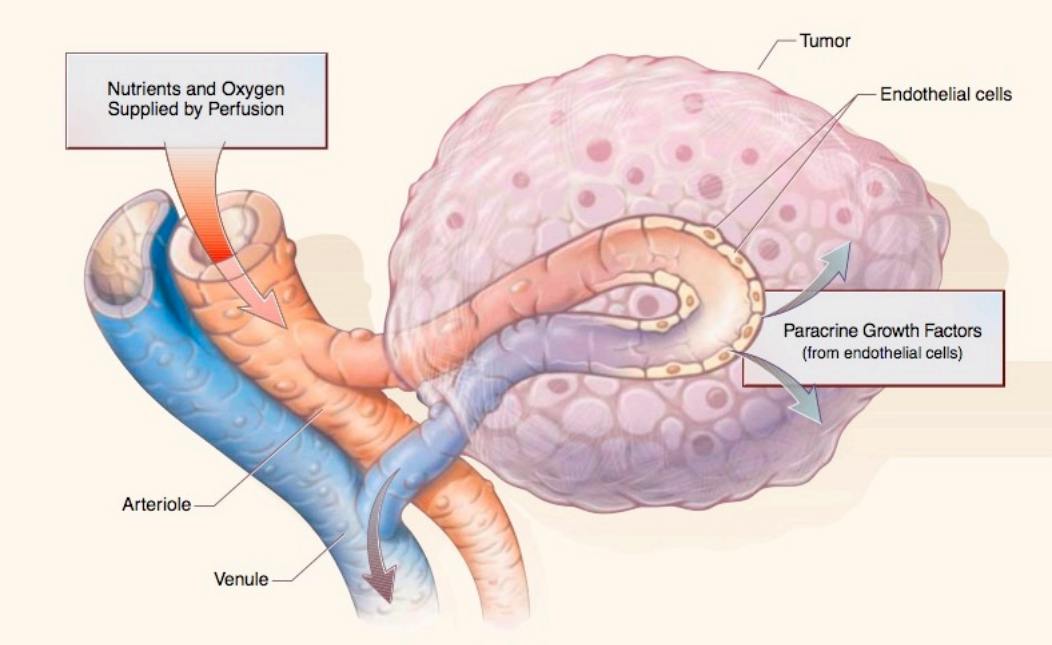
cortistatin K: R = H, **3.9**
cortistatin L: R = OH, **3.10**

3.2 BIOLOGICAL ACTIVITY OF THE CORTISTATINS

Members of the cortistatin family exhibit antiangiogenic properties against human umbelicial vein endothelial cells (HUVECs). Angiogenesis, which is the process of capillary blood vessel generation, is a critical requirement for the growth of solid tumors, as well as the progression of diabetic retinopathy, psoriasis, and rheumatoid arthritis.

Tumors can exist in the human body for months to years without producing symptoms or undergoing rapid growth. However, if at some point the cells within the tumor "switch" to an angiogenic phenotype, the tumor becomes vascularized, which then leads to rapid disease progression via perfusion and paracrine effects.[100, 101] As a result of vascularization, the tumor becomes perfused and thus has an increased access to nutrients and oxygen, as well as an increased efficiency in excreting waste metabolites (Figure 3.3). In addition, paracrine effects are manifested when the capillary endothelial cells, which line the new blood vessels, start producing a variety of growth factors, including fibroblast growth factors, heparin-binding epithelial growth factor, granulocyte colony-stimulating factor, platelet-derived growth factor, and insulin-like growth factor I. These perfusion and paracrine effects work synergistically to increase the growth and proliferation of the tumor.

Figure 3.3 (Source: New England Journal of Medicine)[100]



An additional complication of angiogenesis is that it decreases the responsiveness of tumor cells to traditional chemotherapeutic reagents. This is due to the building of interstitial pressure within the tumor as a result of compressed, leaky blood vessels.

When used in conjunction with traditional chemotherapeutics, antiangiogenics have proven to be very successful in preventing tumor growth. In fact, in some animal studies, the use of antiangiogenics have led to disease elimination.[102] An additional promising factor is that resistance to antiangiogenic agents has not yet been observed.[103] Due to these promising therapeutic characterists, natural products that exhibit antiangiogenesis are of great interest to the medicinal community.

After isolating cortistatins A, B, C, and D, Kobayashi tested these compounds for their activity against several cell lines including: HUVECs; normal human dermal fibroblast (NHDF); and three cancer lines including KB epidermoid carcinoma cells (KB3-1), human chronic myelogenous leukemia cells (K562), and murine neuroblastoma cells (Neuro2A). HUVEC cell lines are the standard cell lines used in testing for antiangiogenic activity

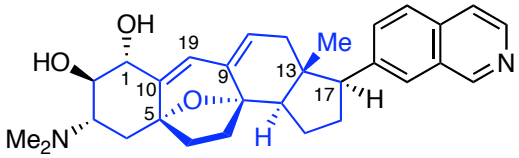
Kobayashi's screenings revealed cortistatin A to be the most biologically active of the cortistatins, exhibiting an IC_{50} of 1.8 nM and a selectivity index of >3000 for HUVECs in comparison to NHDF, KB3-1, K562, and Neuro2A cells. The high selectivity of cortistatin A for HUVECs suggests that its mode of action is an antiangiogenic pathway, rather than one of general cytotoxicity. The second most potent member of the family was determined to be cortistatin J, exhibiting an IC_{50} of 8 nM and a selectivity index of 300–1100 for HUVECs in comparison to NHDF, KB3-1, K562, and Neuro2A cells.

In light of the impressive biological activity possessed by cortistatins A and J, along with the low natural abundance of the cortistatins, these natural products are ideal targets for synthetic organic chemists.

3.3 BUXUS AND CIMICIFUGA ALKALOIDS

The core structure of cortistain A possesses an oxabicyclo[3.2.1]octene moiety contained within a 9(10→19)-*abeo*-androstane skeleton (Figure 3.X). Although the structure is rare, the 9(10→19)-*abeo*-androstane skeleton is not unique and, in fact, is a common motif in the natural products derived from the medicinal plants *Buxus* and *Cimicifuga* sp.

Figure 3.4

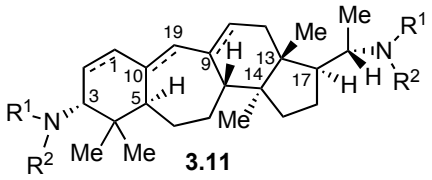


2.1

9(1019)-*abeo*-androstane skeleton indicated in blue

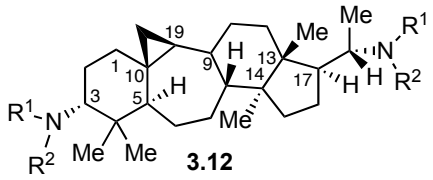
Buxus alkaloids are contained within the family Buxaceae, which belongs to the Euphoribales order. They are classified as triterpenoidal alkaloids that are found natively in a variety of plants and trees, and they have been used as folk medicines throughout Asia for a range of ailments including rheumatism, malaria, gonnorrhoea, and skin infections. They usually contain either a 9(10→19)-*abeo*-14α-methylpregnane skeleton **3.11** or a 9β,19-cyclo-14α-methylpregnane skeleton **3.12** (Figure 3.5).[104] Some have oxygen substitution at C2, C6, C11 or C16, and many vary in their degree of unsaturation. With the exception of a very few cases, they all contain an amino group at C3 and C20, a trans-relationship between the C5-H and C8-H, as well as the C13-Me and C14-Me; and a quaternary center at C4. To date, over 37 natural products with the core structure **3.11** or **3.12** have been isolated from the Buxus plants.

Figure 3.5



3.11

9(10→19)-*abeo*-14α-methylpregnane skeleton



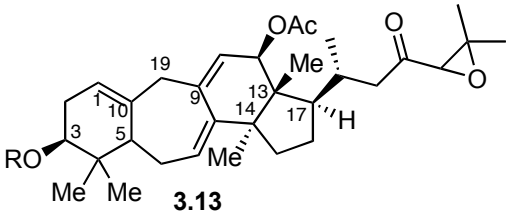
3.12

9β,19-cyclo-14α-methylpregnane skeleton

R^1–R^4 = H, alkyl, acyl

In contrast to the Buxaceae family, only one alkaloid (Figure 3.6) containing the 9(10→19)-*abeo*-androstane skeleton has been isolated from the plants of Cimicifuga.[105] The biological activity of cimicifol (**3.13**) has not been evaluated; however, the plant from which it was extracted, *C. foetida,* has been used in traditional Chinese medicine for anti-inflammatory, antipyretic and analgesic purposes.

Figure 3.6



3.13

R = β-xylosyl

3.4 MARTIN GROUP APPROACH TO CORTISTATIN A

In our retrosynthetic analysis, that is outlined in Scheme 3.1, we identified three key synthetic transformations that would allow for both the facile construction of our target and methodology development. The first key step, an enantioselective conjugate addition employing a furan nucleophile, was entirely unprecedented and would have applications to numerous compounds beyond cortistastin A (see Chapter 2). The second key step, a diastereoselective Diels-Alder cycloaddition employing a highly functionalized furan and a dienophile that serves as an ethylene surrogate, represented an opportunity to broaden existing methodology. Furans are known to be challenging Diels-Alder partners, mainly due to the propensity of the oxabicyclic product to undergo retro-[4+2]

cycloadditions.[106] Furthermore, methods for diastereoselective Diels-Alder rections with masked ethylenes, such as a vinyl sulfoxide wherein the sulfoxide moiety can be reductively removed, are not well-developed and have only been applied to very simple furans with modest to good diastereomeric excess and poor endo/exo ratios.[107] Finally, the cascade RCM key step would be the first example of this reaction with such an advanced and functionalized interemediate.[108] As the use of metathesis is ubiquitous in organic synthesis, having been used frequently on process scale, the extension of this method to more complex substrates would be valuable. Hinging upon these three key synthetic transformations: a cascade RCM to access the core structure, a diastereoselective Diels-Alder reaction, and an enatioselective conjugate addition, our proposed approach would access the natural product in enantiopure form in only 20 steps.

The proposed retrosynthesis begins with a late-stage introduction of the isoquinoline unit via 1,2-addition of 7-bromoisoquinoline to ketone **3.14**, followed by silane promoted ionization of the hydroxyl moiety to provide a carbocationic intermediate. Hydride reduction from the less hindered face of that intermediate would generate compound **2.1** and establish the requisite stereochemistry at C17.[109, 110] Compound **3.14** arises from a *trans* diaxial opening of epoxide **3.15** with an acetate nucleophile. The regioselectivity for this S_N2-like attack is well precedented in the Martin Group.[111] The dimethylamino functional group would arise from removal of the nosyl-protecting group and methylation, using Fukuyama's method.[112]

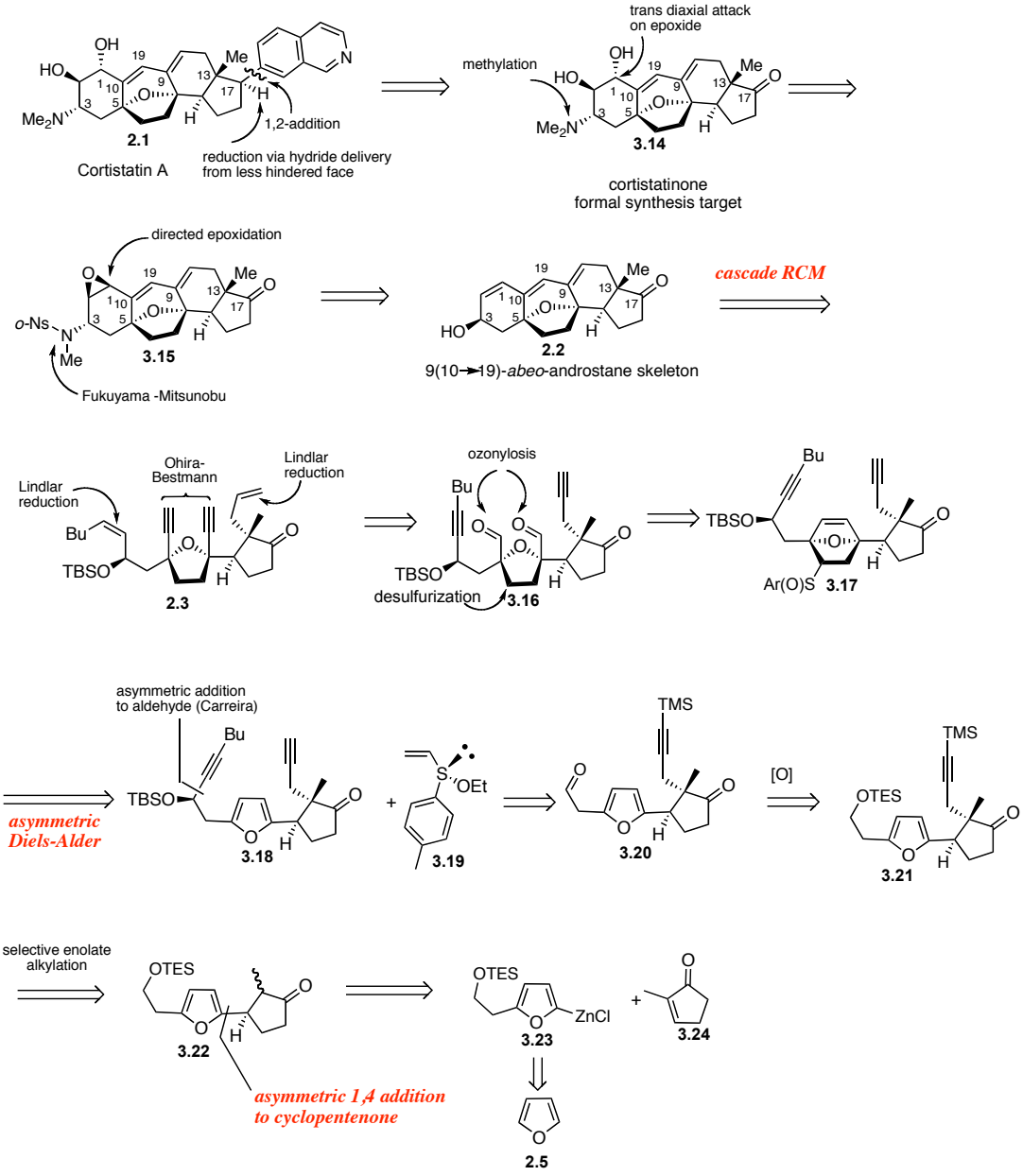
Epoxide **3.15** would arise from an alcohol-directed expoxidation of **2.2**. The amino moiety would then be installed at C3 with a simultaneous sterochemical inversion via the Fukuyama-Mitsunobu protocol.[113] The 9(10→19)-*abeo*-androstane skeleton would arise from a key cascade RCM (right to left) of **2.3**, forming the BCD rings of cortistatin A in a single step. Grubbs catalyst is expected to load onto the more reactive terminal olefin, directing the RCM from right to left. This key transformation, if successful, would represent the first yne-ene-yne cascade RCM on such a highly functionalized substrate,[108] as well as an expeditious route to the 9(10→19)-*abeo*-androstane molecular scaffold.

The RCM precursor **2.3** would be accessed via double Lindlar reduction of **3.16**, followed by an Ohira-Bestmann transformation of both aldehydes into alkynes.[114, 115] The highly substituted tetrahydrofuran **3.16** would arise from the ozonolytic cleavage of oxabicycle **3.17**, which could be obtained from an asymmetric Diels-Alder reaction between furan **3.18** and a chiral vinyl sulfoxide (after desulfurization).[106, 107] There are very few examples of Diels-Alder reactions with highly functionalized 2,5-disubstituted furan substrates, despite the frequent presence of oxabicycles in natural products. Thus, successfully achieving this transformation in the proposed cortistatin synthesis would broaden existing methodology.

The Diels-Alder precursor **3.18** is a 2,5-disubstituted furan containing three chiral centers. The chiral center at the propargylic carbon could be constructed from an asymmetric addition of an acetylide fragment to aldehyde **3.20** using chemistry developed by Carriera.[116-118] The remaining two chiral

centers are contained within the cyclopentanone ring, but there is no known method for synthesizing this compound enantioselectively. Constructing **3.22** requires an asymmetric 1,4-addition of furan derivative **3.23** to 2-methylcyclopentenone, a transformation for which there was no precedent. Subsequent enolate alkylations, with the methylation occurring first, should provide the desired compound **3.21** with the propargyl moiety *trans* to the furan.

Scheme 3.1


OH
HO
Me
N
Me2N
2.1
Cortistatin A
1,2-addition
reduction via hydride delivery
from less hindered face
trans diaxial attack
on epoxide
methylation
3.14
cortistatinone
formal synthesis target
directed epoxidation
o-Ns
N
Me
3.15
Fukuyama -Mitsunobu
cascade RCM
2.2
9(10→19)-abeo-androstane skeleton
Lindlar
reduction
Ohira-
Bestmann
Lindlar
reduction
Bu
TBSO
2.3
ozonylosis
desulfurization
3.16
Ar(O)S
3.17
asymmetric addition
to aldehyde (Carreira)
asymmetric
Diels-Alder
3.18
OEt
3.19
TMS
3.20
[O]
OTES
3.21
selective enolate
alkylation
3.22
asymmetric 1,4 addition
to cyclopentenone
ZnCl
3.23
3.24
2.5

3.5 CONCURRENT SYNTHETIC APPROACHES TO CORTISTATIN A

At the time that we initiated our studies, there were no reported syntheses of cortistatin A. However, due to the impressive biolgoical properties of this natural product, several research groups have been working towards syntheses of cortistatin A. Consequently, and concurrently with our research, numerous partial and full synthetic approaches have been published. Despite the large number of publications to date, however, our synthetic approach remains both novel and competitive. Additionally, none of the problems we identified in our retrosynthetic analysis have been addressed by any of the published syntheses.

3.5.1 Total Syntheses

Only three total syntheses have been reported to date. The first total synthesis of (+)–cortistatin A was reported by Baran in 2008.[119] This report was followed shortly thereafter by syntheses from Nicolaou and Shair.[120, 121]

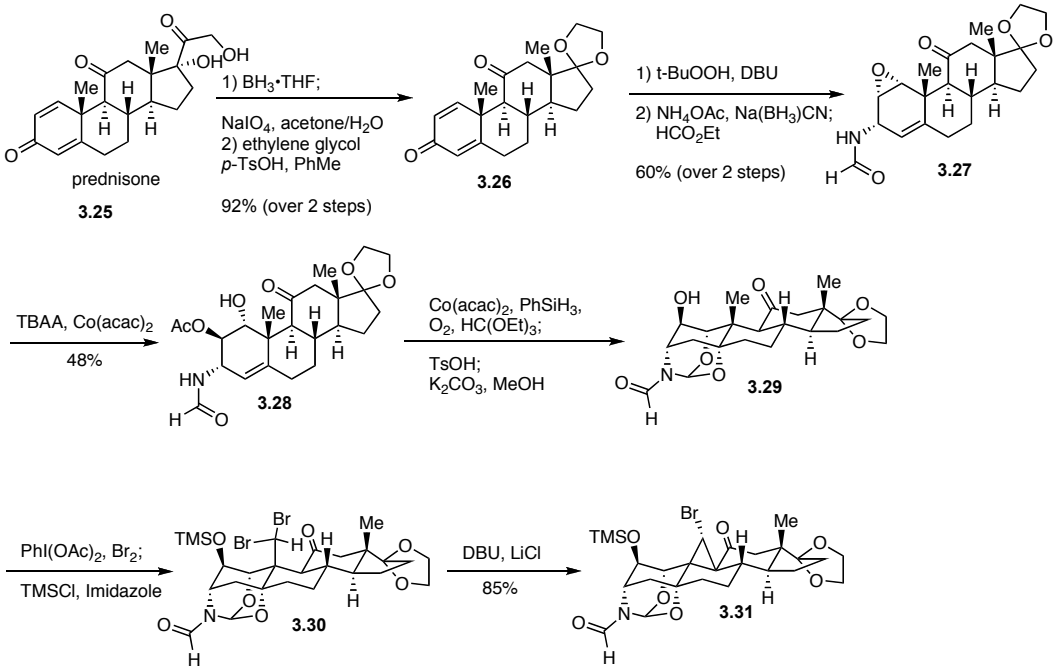
3.5.1.1 Baran's Total Synthesis of (+)–Cortistatin A

Although technically a total synthesis, Baran's synthesis of cortistatin has also been characterized as a semi-synthesis, because of his use of the very highly functionalized starting material, prednisone (**3.25**). Prednisone is a commerically available corticosteroid that costs approximately $1/gram. Baran's approach capitalizes upon the inherent stereochemistry and functionality in prednisone in order to achieve an efficient and enantioselective synthesis of cortistatin A.

Beginning with prednisone, Baran utilized a two-step sequence involving selective borane reduction of the alpha-hydroxy ketone, sodium periodate cleavage of the resultant diol, and carbonyl protection to give **3.26**. Epoxidation

of **3.26** from the less hindered face was effected with t-butyl hydroperoxide, and reductive animation and *N*-formylation produced **3.27**. Opening of the epoxide with tetrabutylammonium acetate furnished **3.28**. Hydration of the trisubstituted olefin, reaction of the intermediate with triethylformate, and *in situ* solvolysis of the acetate afforded **3.29**. The angular methyl group was dibromonated via the assistance of a neighboring oxygen-centered radical, and a subsequent S_N2 reaction furnished cyclopropyl intermediate **3.31** and setting the stage for the key cascade step (Scheme 3.2).

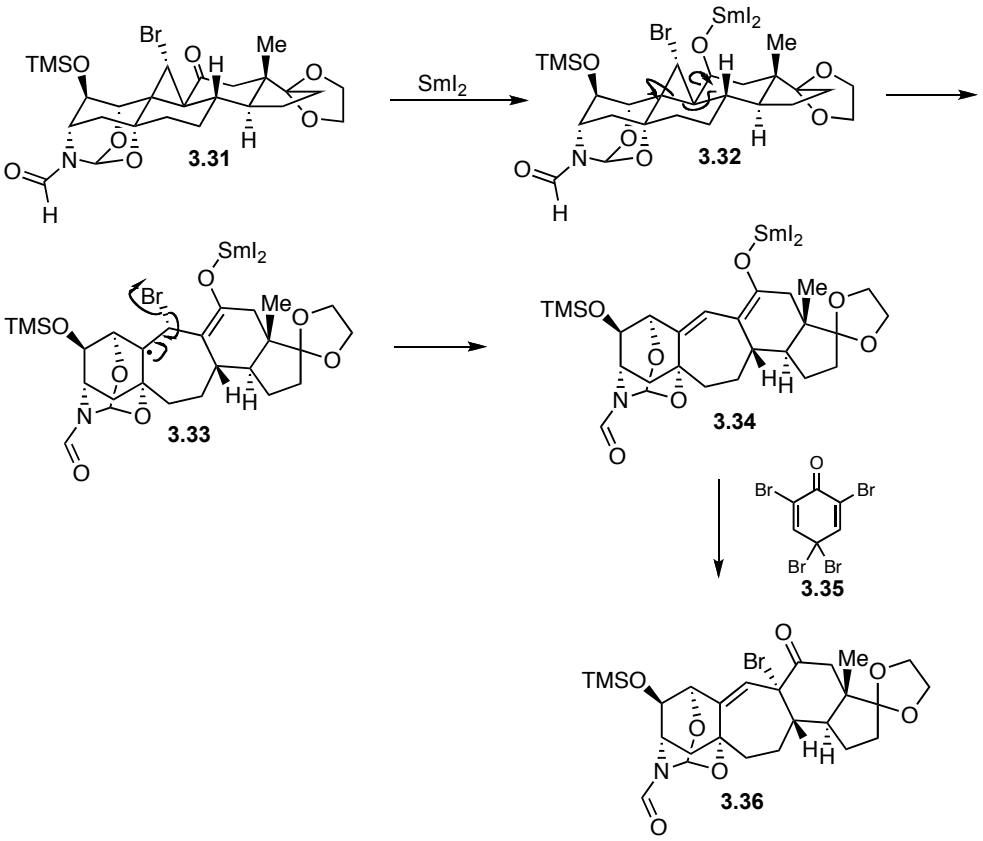
Scheme 3.2



Reaction of **3.31** with SmI_2 generated a samarium stabilized ketyl radical, which underwent a cyclopropane ring opening to afford samarium enolate **3.33**. Homolytic cleavage of the carbon-bromine bond afforded the conjugated the di-

enolate **3.34**, which was trapped at the alpha position with an electrophilic bromine source (Scheme 3.3).

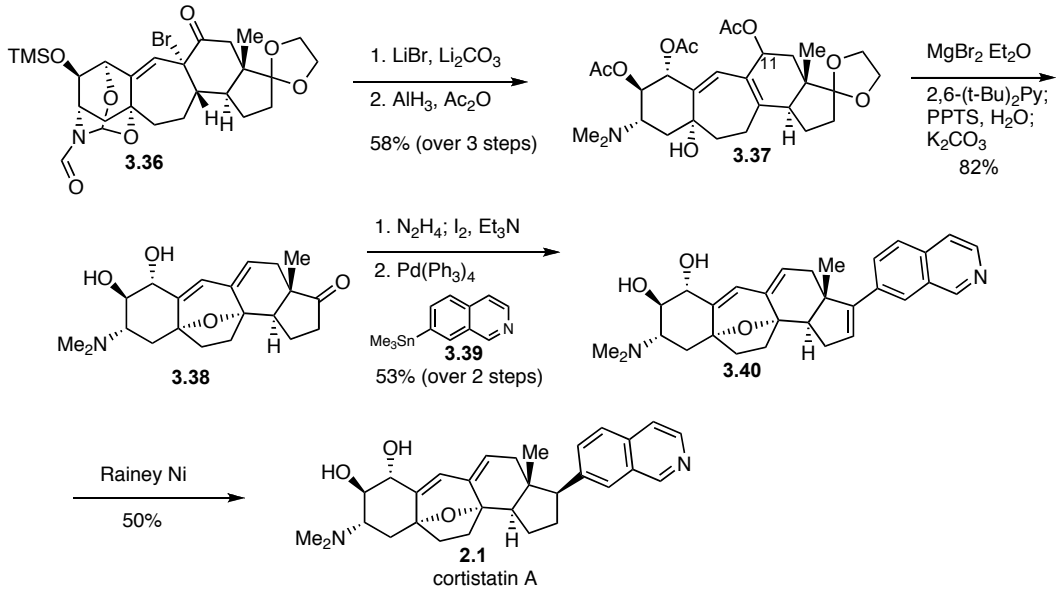
Scheme 3.3



Baran's endgame was intiated with E_2 elimination of bromide ion from **3.36** using lithium carbonate. Reduction of the orthoamide and ketone fuctions with alane and subsequent acetylation gave the late-stage intermediate **3.37**. The oxabicycle was then formed via S_N2' displacement of the C11 acetate. Following deprotection of the cyclopentanone group, **3.38** was transformed into an alkenyl iodide via an intermediate hydrazone. The final two steps of the synthesis utilized

a Stille coupling with isoquinoline **3.39** and a chemoslective reduction to yield cortistatin A in 1.5% overall yield (3.0% BRSM) and 21 steps (Scheme 3.4).

Scheme 3.4



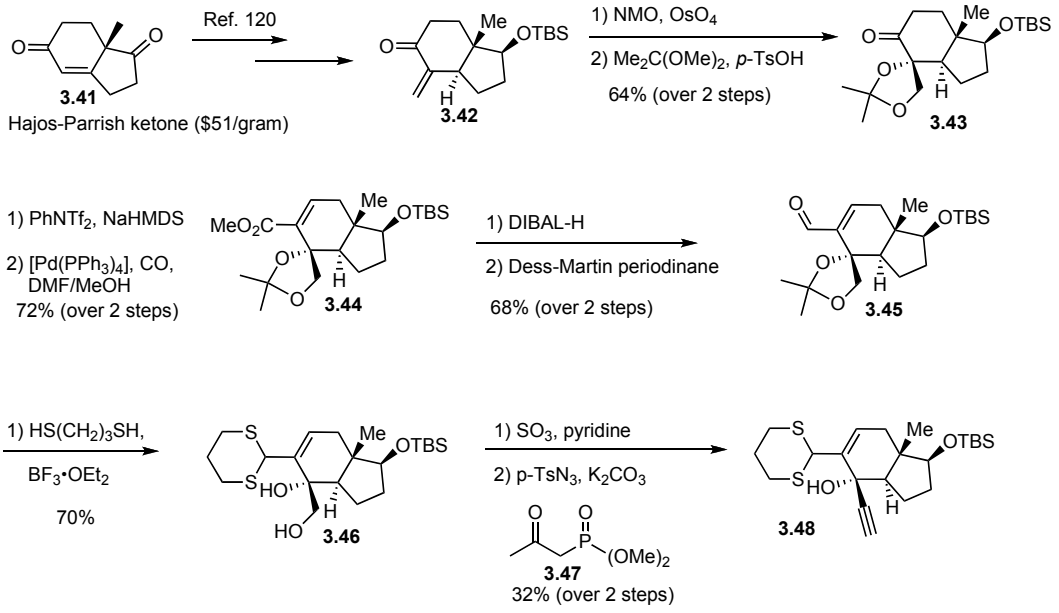
While Baran's approach is certainly impressive, one major drawback is that the chemistry developed is heavily directed by the starting material, prednisone, and is therefore not generalizable to simpler systems. As a result, while Baran has provided an elegant solution to the problem of cortistatin A, he has not developed methodological solutions that are likely to have an impact beyond this particular natural product.

3.5.1.2 Nicolaou's Total Synthesis of (+)–Cortistatin A

Nicolaou's total synthesis of (+)–cortistatin A, which was published approximately five months after Baran's report, utilized the commercially available Hajos-Parrish ketone (**3.41**) as the starting material.[120] Using a five step

protocol developed by Danishefsky,[122] Nicolaou transformed the Hajos-Parrish ketone into **3.42**. Employing the stereochemistry inherent in the molecule to direct the dihydroxylation of the exocyclic double bond**,** a diol was furnished stereoselectively and protected to furnish **3.43**. Subsequent enolate formation and trapping with $PhNTf_2$ produced a vinyl triflate that was converted to the ester **3.44** via a palladium-catalyzed caboxymethylation. Reduction of **3.44** to the alcohol and oxidation produced the aldehyde **3.45.** Protection of the aldehyde as its dithiane followed by oxidation employing the Parikh-Doering protocol gave an intermediate aldehyde that was transformed into the acetylene **3.48** by treatment with the Ohira-Bestman reagent (Scheme 3.5)**.**

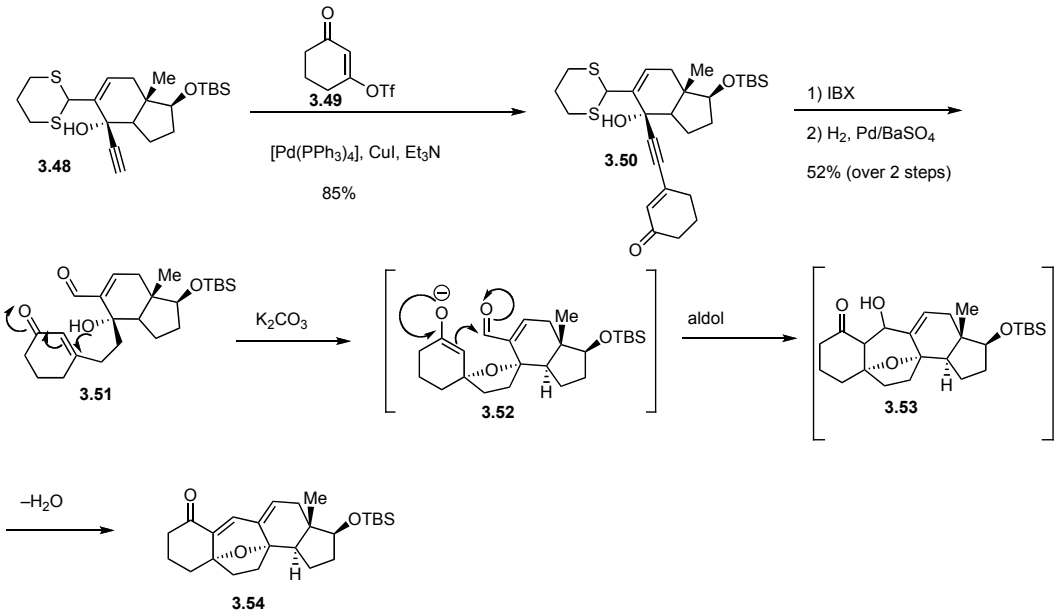
Scheme 3.5



Following another palladium-catalyzed coupling with **3.49**, reduction of the alkyne, and deprotection of the aldehyde produced **3.51**, setting the stage for

Nicolaou's key step. Using K_2CO_3, a cascade sequence was initiated with the formation of a tetrahydrofuran ring via a Michael addition. The intermediate enolate participated in an intramolecular aldol condensation and dehydration sequence to produce **3.54**, in which all four rings of cortistatin A were in place (Scheme 3.6).

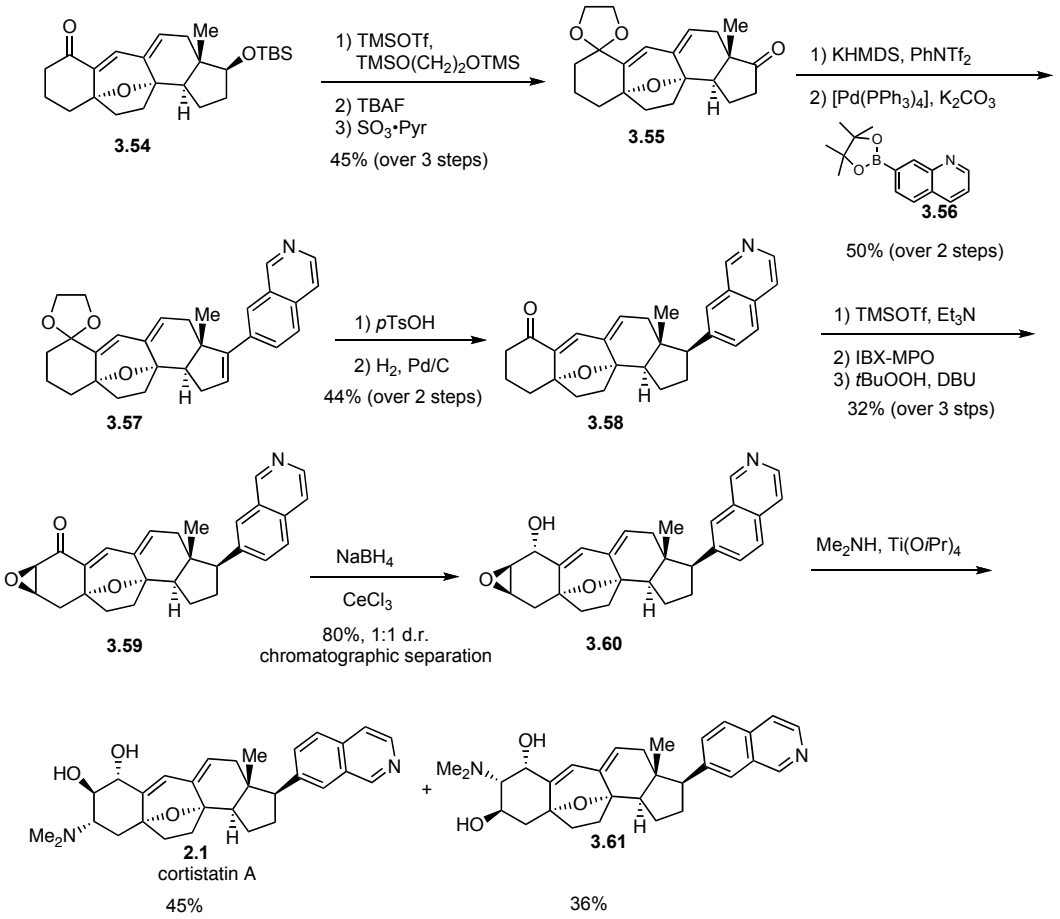
Scheme 3.6



Completion of the synthesis involved functional manipulation of the A and D rings (Scheme 3.7). Beginning with a series of protection, deprotection, and oxidation steps, **3.54** was transformed into cyclopentanone **3.55**. Vinyl triflate formation and subsequent Suzuki-Miyaura coupling to install the isoquinoline furnished **3.57**. Reduction of the cyclopentene double bond proceeded chemoselectively to afford **3.58**. From **3.58** a TMS enol ether was formed, which underwent subsequent oxidation to an enone. Epoxidation of the enone furnished

3.59. The reduction of the cyclohexanone proceeded without any stereoselectivity, furnishing a disappointing mixture (1:1) of diastereomers. The final step, an epoxide opening, also proceeded in poor regioselectivity, giving a mixture (1.25:1) of isomers.

Scheme 3.7



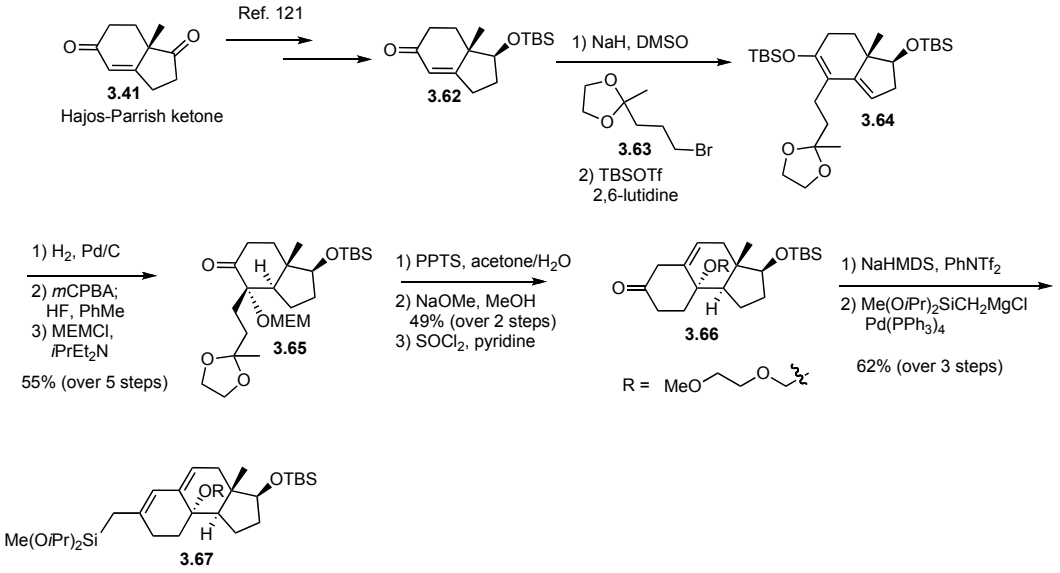
Beginning from the Hajos-Parrish ketone **3.41**, Nicolaou's synthesis required 32 steps and proceeded in 0.009% yield. The highlight of the synthesis is certainly the key cascade sequence to construct the oxabicycle moiety.

Although earlier steps in the synthesis proceed smoothly, Nicolaou's synthesis suffers from disappointing diastereoselectivity and regioselectivity in the final steps, drastically lowering the overall yield and practicality of the synthesis.

3.5.1.3 Shair's Total Synthesis of (+)–Cortistatin A

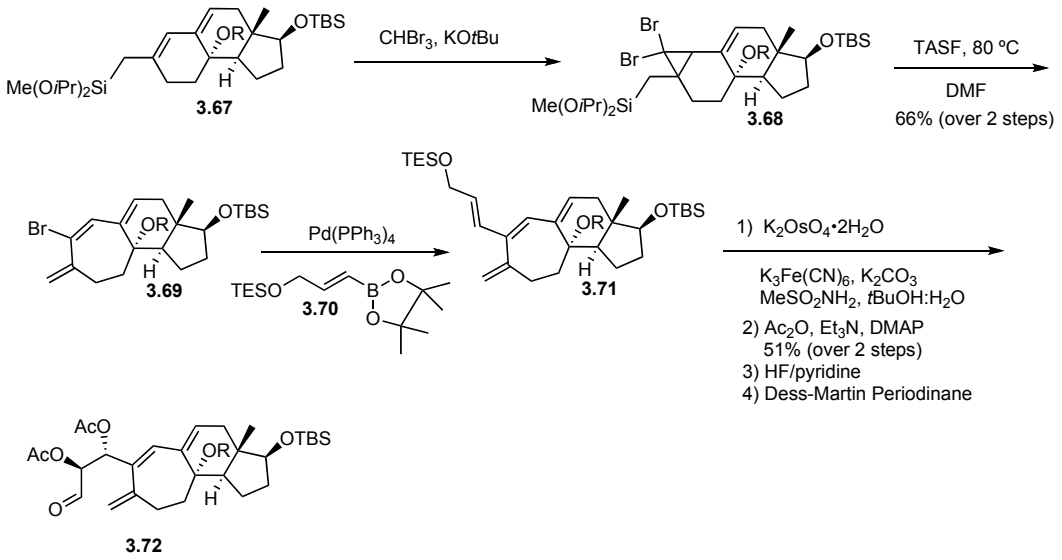
Like Nicolaou, Shair also began his synthesis of (+)–cortistatin A with the Hajos-Parrish ketone (**3.41**). Borrowing from the same Danishefsky protocol as did Nicolaou, Shair accessed **3.62** in two steps.[121] Deprotonation at the γ-position of the α,β-unsaturated ketone **3.62** using a dimsyl anion and subsequent alkylation at the alpha-position with **3.63** occurred smoothly. Preparation of the TBS silyl enol ether, arising from trapping of the thermodynamic enolate, produced **3.64**. Diastereoselective hydrogenation of **3.64**, followed by a Rubottom oxidation and alcohol protection furnished **3.65**. Unmasking of the ketone function in **3.65** and aldol condensation, followed by $SOCl_2$-mediated elimination furnished **3.66**. Selective enolate formation and trapping with phenyltriflimide afforded a vinyl triflate, which was transformed into allyl silane **3.67** via a palladium catalyzed-cross coupling (Scheme 3.8).

Scheme 3.8



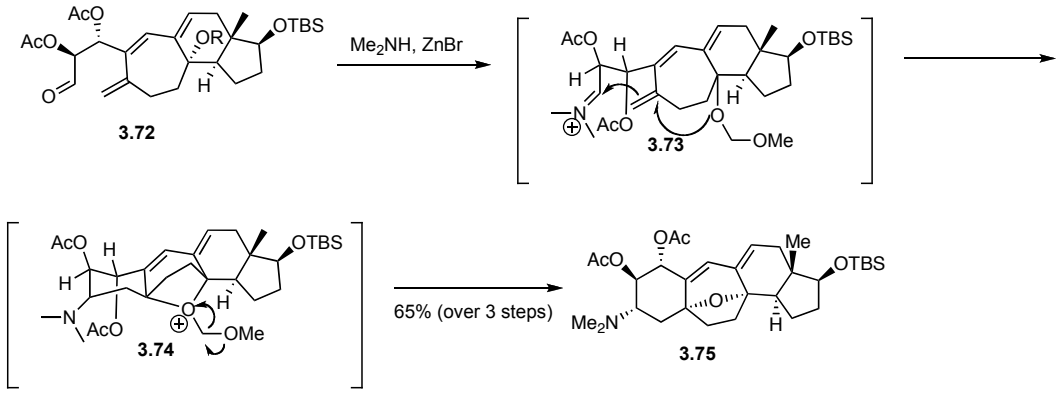
Chemoselective cyclpropanation of **3.67** with dibromocarbene, followed by fluoride-mediated ring expansion furnished **3.69**. Tetraene intermediate **3.71** was formed via palladium-catalyzed coupling between vinyl bromide **3.69** and vinyl boronate ester **3.70**. Dihydroxylation of **3.71** proceeded with excellent selectivity at the trans-disubstituted double bond only, in a 10:1 dr. Protection of the resultant diol and desilylation followed by oxidation of the primary aldehyde provided **3.72** (Scheme 3.9).

Scheme 3.9



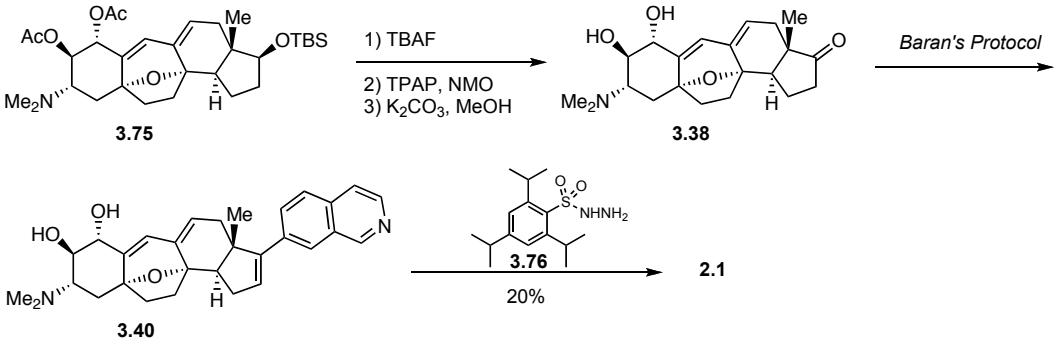
With aldehyde **3.72** in hand, Shair successfully executed the key step of his synthesis, an aza-Prins cyclization (Scheme 3.10) In the presence of dimethylamine and zinc bromide, intermediate iminium **3.73** was presumably formed. Shair postulated that the minimization of $A^{1,3}$-strain led to the preference for chair conformation **3.74**, which upon cyclization leads to the product **3.75** (Scheme 3.10).

Scheme 3.10



Following interception of Baran's cyclopentanone intermediate **3.38**, Shair reproduced Baran's chemistry to complete all but the very last reduction step, in which he employed triisopropylbenzenesulfonyl hydrazide **3.76** to produce cortistatin A in 20% yield (Scheme 3.11).

Scheme 3.11



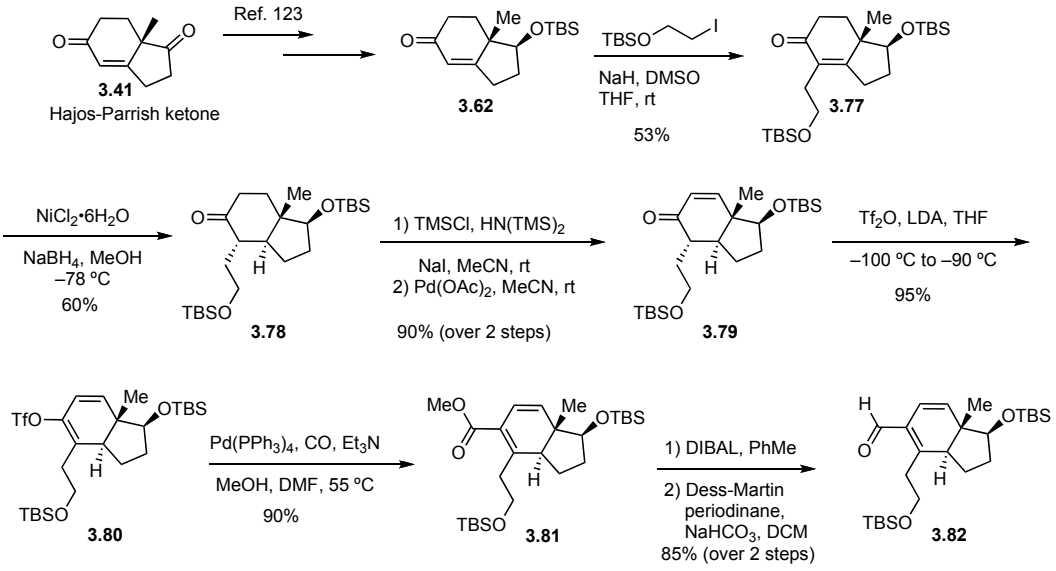
Shair's total synthesis proceeds in 26 steps and 0.14% overall yield from the Hajos-Parrish ketone **3.41**. The highlight of Shair's synthesis is the aza-Prins cyclization, which occurred with excellent diastereoselectivity. In light of the replication of Baran's chemistry in the last three of four steps, coupled with the extremely low 20% yield for the final reduction, which is much lower than Baran's conditions, Shair's approach is best regarded as a formal synthesis, rather than a total synthesis.

3.5.2 Formal Syntheses

Hirama and coworkers published a formal synthesis of cortistatin A in two parts, the first part detailing the synthesis of the core with all four rings intact, and the second detailing elaboration of that core to Nicolaou's advanced intermediate **3.58**.[123, 124]

Beginning with the same starting material as Shair, which was derived from the (+)–Hajos-Parrish ketone **3.41** using known chemistry, Molander's conditions[125] were employed to alkylate the enone, furnishing indanone **3.77**. A stereoselective reduction of **3.77** with $NiCl_2/NaBH_4$ furnished the *trans*-fused ketone **3.78**.[126] Selective TMS enol ether formation, followed by oxidation using Saegusa's conditions provided **3.79** in excellent yield. Transformation of **3.80** into a vinyl triflate and subsequent palladium-catalyzed methoxycarbonylation afforded diene **3.81**. Reduction of the ester moiety to an aldehyde was performed using a two-step protocol to give **3.82** (Scheme 3.12).

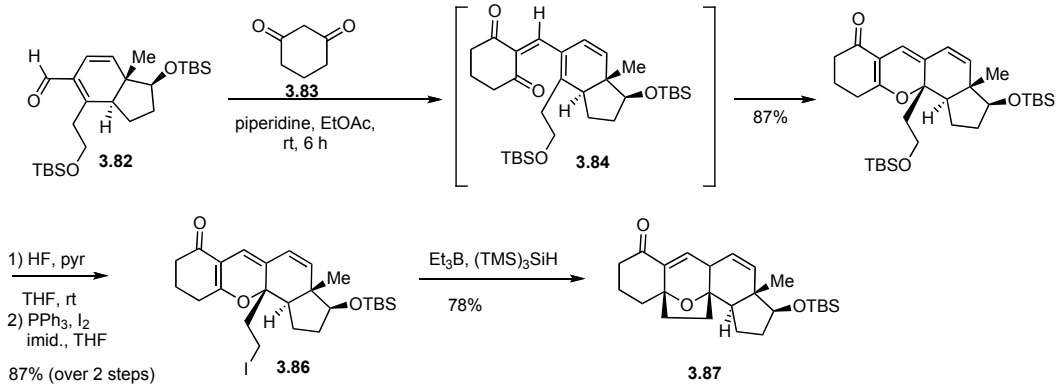
Scheme 3.12



With both C and D rings intact, elaboration of intermediate **3.82** to the tetracyclic core of the natural product took place in four steps. A Knoevenagel reaction between **3.82** and cyclohexane-1,3-dione afforded **3.84**, which underwent a spontaneous 6π–electrocyclization to afford **3.85** in 5:1 dr. Conversion of **3.85**

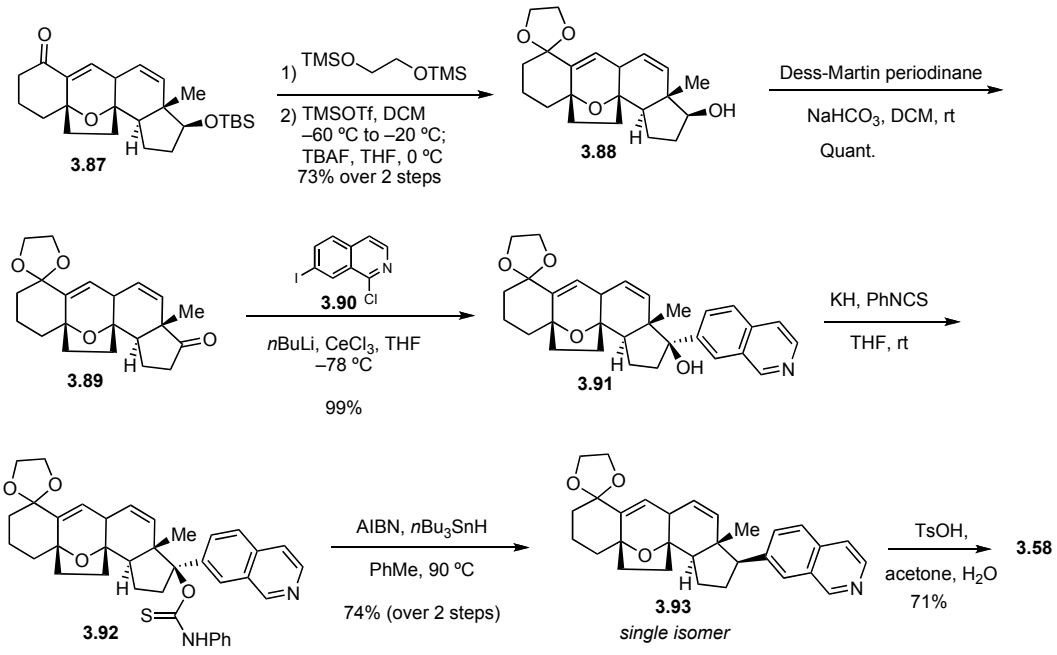
into alkyl iodide **3.86** occurred smoothly and in good yield. The oxabicycle was formed via radical cyclization in 78% yield (Scheme 3.13).

Scheme 3.13



In a separate publication, Hirama reported elaboration of the core structure **3.87** to Nicolaou's advanced intermediate **3.58** in seven steps (Scheme 3.14). Following protecting group manipulation and oxidation of the secondary alcohol, the isoquinoline unit was added via 1,2-addition to the cyclopentanone carbonyl. Screening of reagents led to the discovery that the organocerium reagent derived from **3.90** in the presence of BuLi and cerium chloride afforded an excellent yield of the desired product. A modified Barton-McCombie radical deoxygenation occurred with concomitant chloride removal to yield **3.93** as a single isomer. Ketone deprotection furnished Nicolaou's intermediate **3.58**.

Scheme 3.14



Hirama accessed the core of cortistatin A in 14 steps and 12.3% overall yileld. His formal synthesis, beginning with the Hajos-Parrish ketone, proceeded in 22 steps and 4.6% overall yield. Factoring in Nicolaou's endgame, a total synthesis of cortistatin A employing Hirama's approach would proceed in 27 steps and 0.27% overall yield. The highlight of Hirama's synthesis is the key Knoevenagel/electrocyclization sequence which forms both C and D rings in one step and in excellent yield. Additionally, the installation of the isoquinoline was much higher yielding than Baran's protocol, although it is unknown if the isoquinoline cerium reagent would be compatible with the uprotected hydroxy groups present in Baran's advanced intermediate **3.38**.

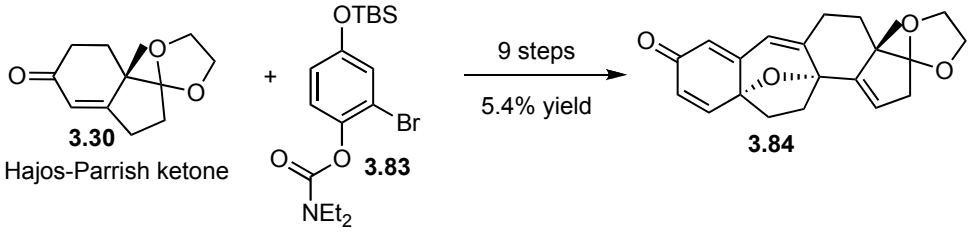
3.5.3 Partial Syntheses

The largest body of work in this area has been on partial syntheses of cortistatin A. Due to the complexity of the natural product and the impressive biological activity which calls for examination of simpler analogs, efforts have been focused on synthesizing either the core or partial core of cortistatin A.

3.5.3.1 Danishefky's Synthesis of the (+)–Cortistatin A Core

Beginning with the Hajos-Parrish ketone and aryl bromide **3.94**, Danishefsky and coworkers accessed the full core of cortistatin A in only nine steps and 5.4% overall yield (Scheme 3.15).[122] All four rings and three of the eight requisite stereocenters were established.

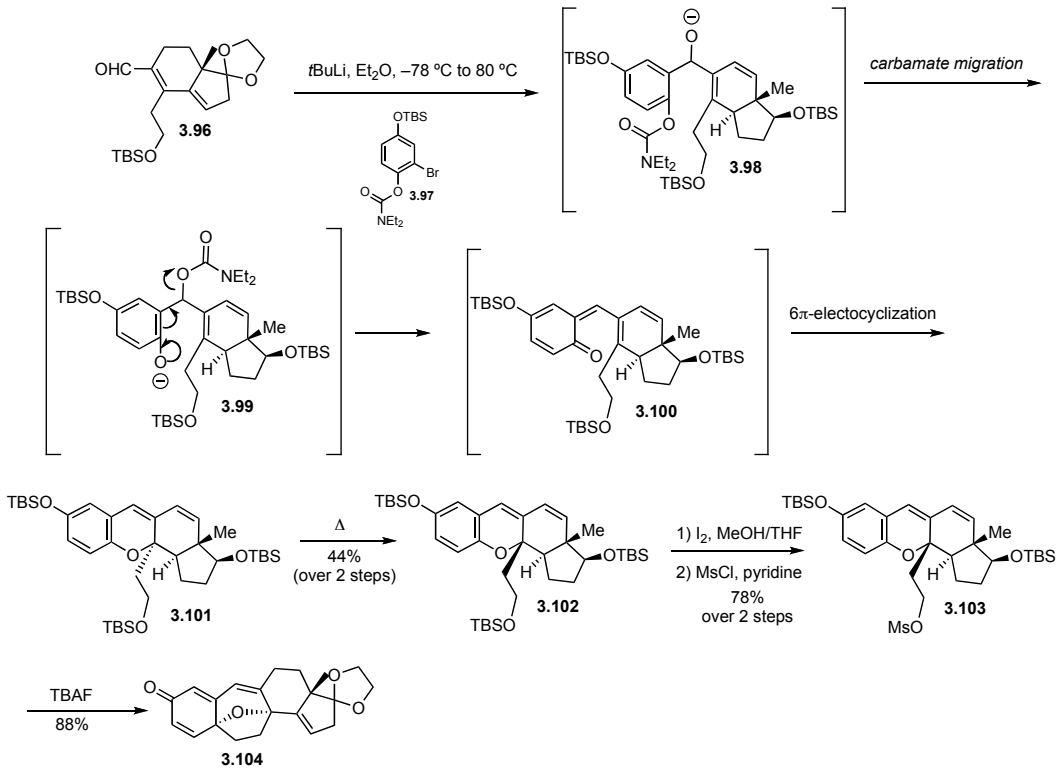
Scheme 3.15



Highlights of the synthesis include a cascade sequence similar to that reported by Hirama, in which addition of the aryllithium reagent derived from aryl bromide **3.97** added to aldehyde **3.96**; subsequent migration of the carbamate afforded quinone methide **3.100**. Spontaneous 6π–electrocyclization occurred to yield the tetracycle **3.101**, but with the wrong stereochemistry. However, upon heating, **3.101** underwent epimerization to yield the desired stereoisomer, presumably through a retro 6π-pathway. The mesylated alcohol **3.103** was

formed in two steps and 78% overall yield. The final step involved a fluoride-mediated alkylative dearomatization to access **3.104** (Scheme 3.16).

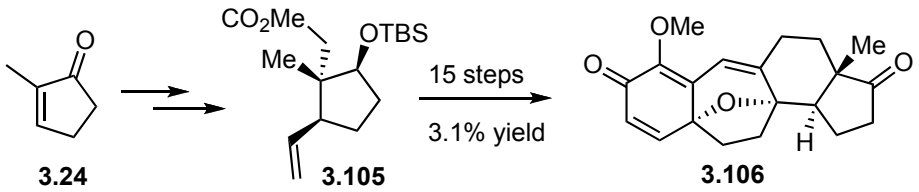
Scheme 3.16



3.5.3.2 Sarpong's Synthesis of the (+)–Cortistatin A Core

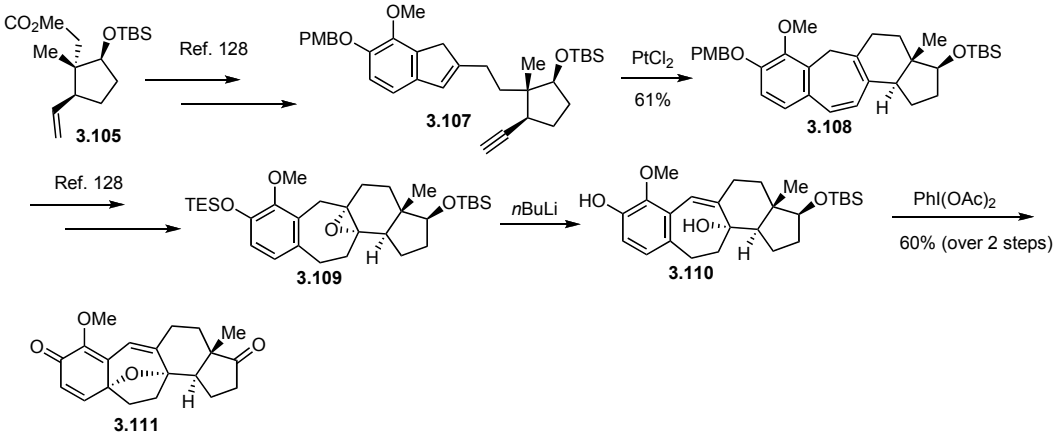
Sarpong and coworkers reported a synthesis of the racemic core of cortistatin A, which proceeded in 15 steps and 3.1% overall yield from commercially available starting materials (Scheme 3.17).[127]

Scheme 3.17



Highlights from the synthesis include a key $PtCl_2$-catalyzed cycloisomerization to form the seven-membered C ring.[128] Further functionalization of the C ring proceeded via epoxide intermediate **3.109**. Base-mediated epoxide opening, followed by an oxidative dearomatization promoted by hypervalent iodine furnished the core **3.111** (Scheme 3.18).

Scheme 3.18

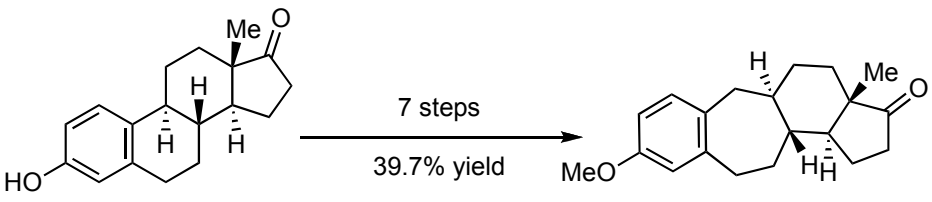


An important advantage of this approach is that the advanced starting material **3.105** has previously been made in enantiopure form by Oppolzer,[129] allowing this route to be easily adapted to an enantioselective synthesis.

3.5.3.3 Corey's Synthesis of the (+)–Cortistatin A Core

Corey published a semisynthetic approach to a minimal carbocyclic core of cortistatin A that started from (+)-estrone and proceeded in seven steps and 39.7% overall yield to furnish **3.113** (Scheme 3.19).[130]

Scheme 3.19

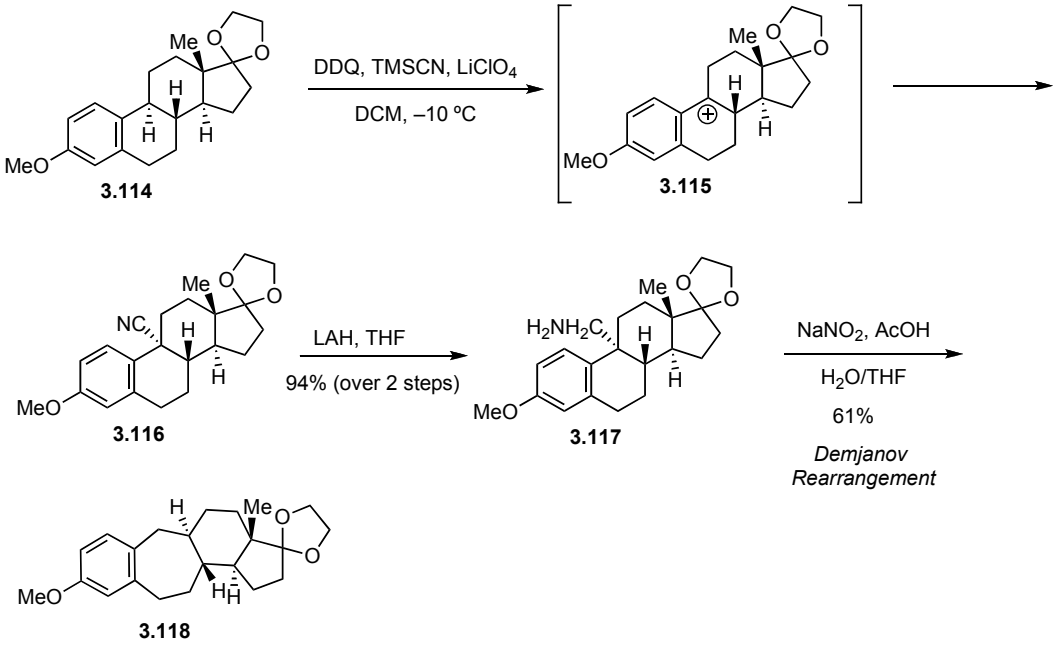


3.112
(+)-estrone

3.113

Key steps from the synthesis include a benzylic oxidation step to install a cyanide functional handle, which was then reduced to a primary amine and submitted to a Demjanov rearrangement in the presence of nitrous acid (Scheme 3.20)

Scheme 3.20

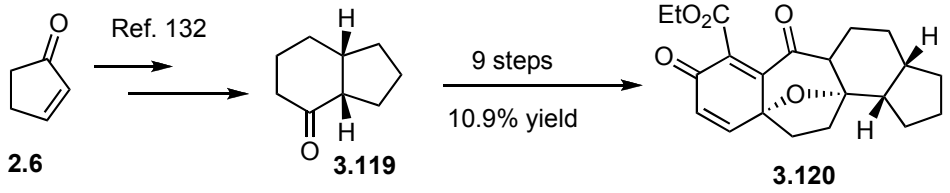


While this core structure could not be elaborated to cortistatin A in any practical sense, Corey utilized it for the preparation of cortistatin A-inspired analogs, some of which proved to exhibit remarkable antiangiogenic activity.[131]

3.5.3.4 Yang's Synthesis of the (+)–Cortistatin A Core

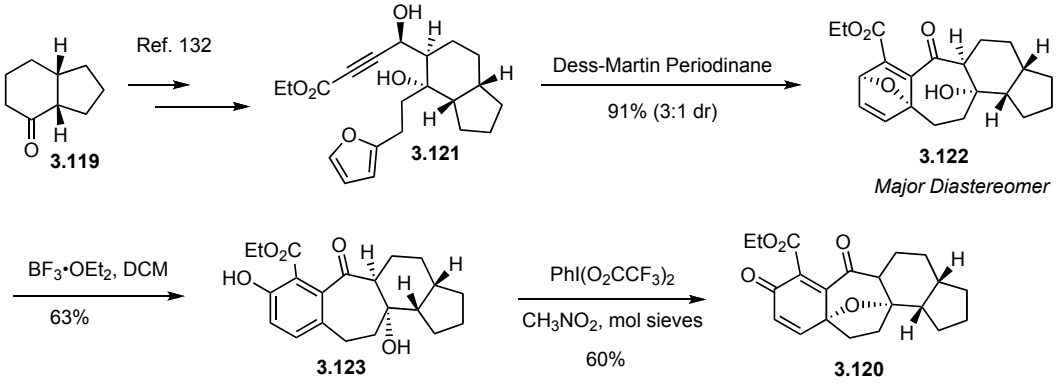
Yang and coworkers reported a synthesis of a core of cortistatin A, which proceeded in eight steps and 10.9% overall yield (Scheme 3.21).[132] The starting material (**3.119**) was an enantiopure compound that had been synthesized previously.[133]

Scheme 3.21



Key steps include an intramolecular Diels-Alder reaction of a furan to form both C and D rings of the core, followed by an acid-catalyzed ring opening of **3.122** to furnish phenol **3.123**. The final step employed chemistry almost identical to that used in Sarpong's synthesis, namely a hypervalent iodine-mediated dearomatization to form oxabicycle **3.120** (Scheme 3.22).

Scheme 3.22

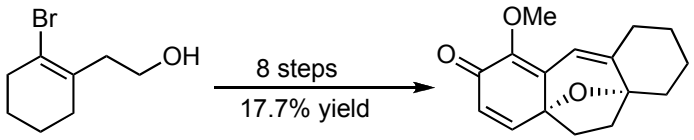


Although all four rings are constructed in Yang's synthesis, it is unlikely that **3.120** can be transformed into cortistatin A, due to the absence of functionality in both the A and B rings. While the intramolecular Diels-Alder and subsequent ring opening is impressive, the novelty of the final sequence is undermined by Sarpong's prior publication employing similar hypervalent iodine chemistry.

3.5.3.5 Danishefsky's Synthesis of a Minimal Cortistatin Core

In a second publication, Danishefsky described a slightly different approach to the BCD ring core of cortistatin A. Beginning from known compound **3.124**, the BCD rings were formed in eight steps and 17.7% overall yield (Scheme 3.23).[134]

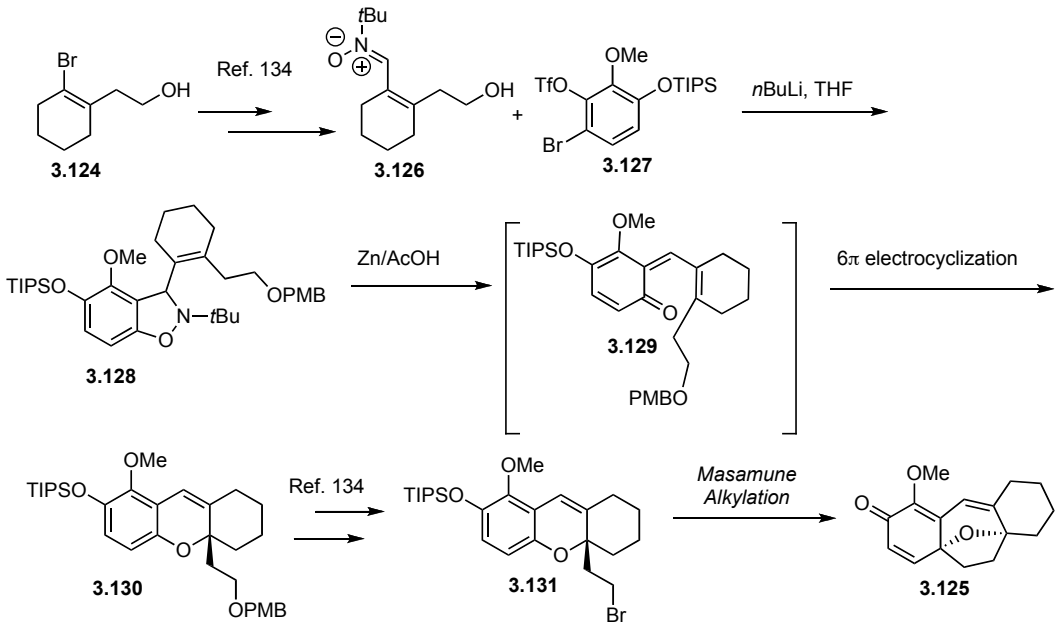
Scheme 3.23



3.124 **3.125**

The key step in this short sequence was a [3+2] cycloaddition between nitrone **3.126** and the benzyne generated from **3.127**. Danishefsky postulated that the regioselectivity of this cycloaddition is controlled by the electron-donating methoxy group *ortho* to the aryne, via an induced polarization of the reactive frontier orbitals of the aryne. The cycloadduct was reduced with Zn/AcOH and an intermediate was intercepted (**3.129)** that was almost identical to intermediate **3.100** in Danishefsky's earlier reported synthesis. Danishefsky also used the same endgame as reported previously, submitting this intermediate to an electrocyclization/alkylation sequence to furnish **3.125** (Scheme 3.24).

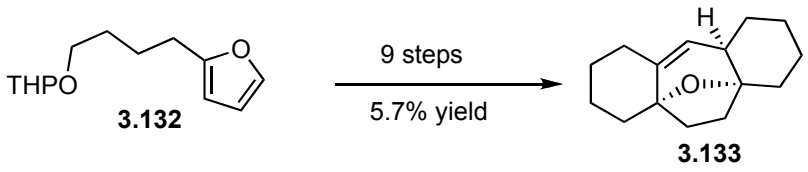
Scheme 3.24



3.5.3.6 Gung's Synthesis of a Minimal Cortistatin Core

Gung reported a synthesis of a racemic BCD ring framework of the cortistatin core. Starting from furan **3.132**, the sequence proceeded in eight steps and 5.7% overall yield (Scheme 3.25).[135]

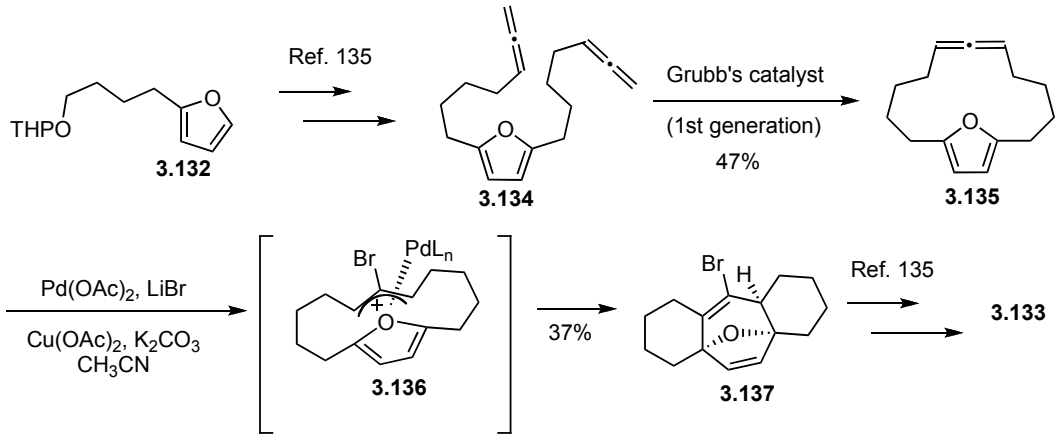
Scheme 3.25



Key steps in Gung's synthesis include an RCM to form a macrocyclic allene **3.134** and a palladium-catalyzed [4+3] cycloaddition, which Gung postulated proceeded via the cationic π-allyl intermediate **3.136** (Scheme 3.26). The cycloaddition is somewhat novel, but suffers from a low yield. Furthermore,

the lack of functionality of core structure **3.133** makes it impractical for elaboration to cortistatin A.

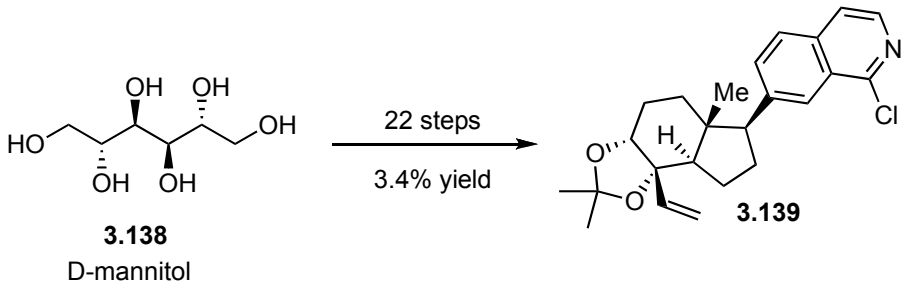
Scheme 3.26



3.5.3.7 Kobayashi's Synthesis of the AB rings of the Cortistatin Core

Kobayashi reported a 22 step synthesis of the AB ring core of cortistatin A, starting from commercially available D-mannitol (Scheme 3.27) that proceeded in 3.4% overall yield.[136]

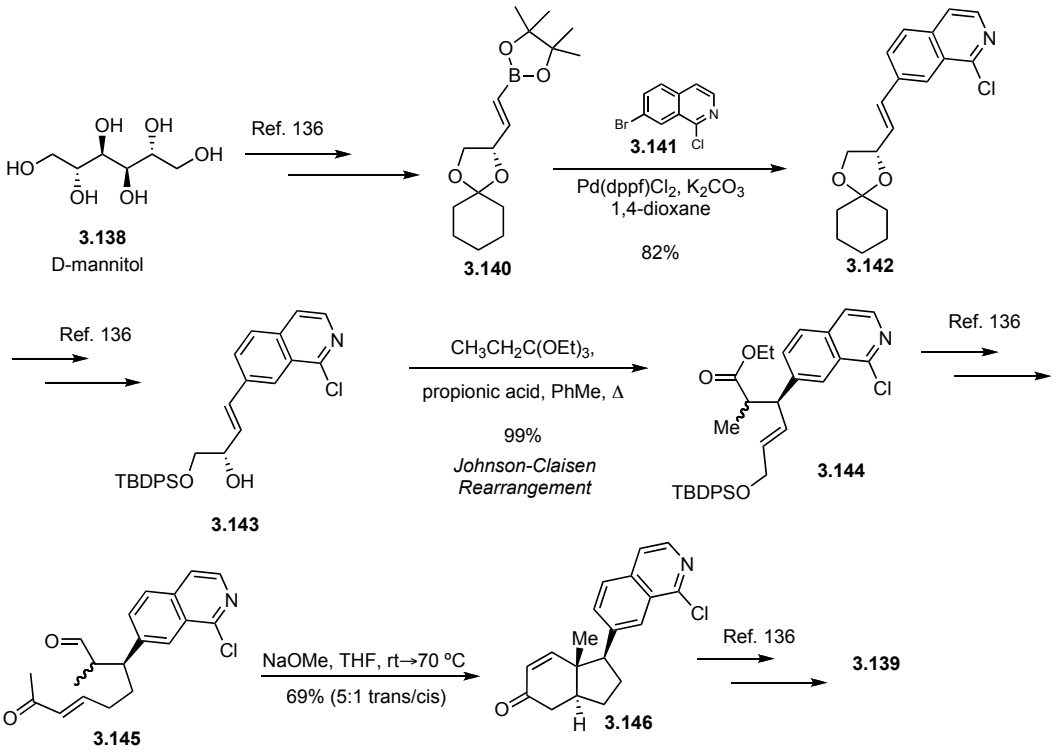
Scheme 3.27



Highlights of the synthesis include a Suzuki cross-coupling between the vinyl boronate ester **3.140** and 7-bromo-1-chloroisoquinoline **3.141**, followed by a

Johnson-Claisen rearrangement to establish the correct stereochemistry at the isoquinoline-bearing carbon. The AB rings were constructed via a Michael-aldol double cyclization that proceeded with 5:1 trans/cis selectivity to furnish **3.146** in moderate yield (Scheme 3.28).

Scheme 3.28

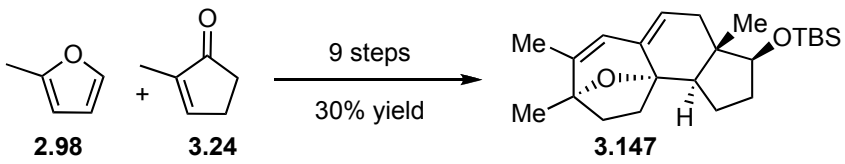


The major disadvantage in Kobayshi's approach is its length. In fact, Kobayashi's synthesis of the AB core is lengthier than Baran's total synthesis of cortistatin A. In addition, Kobayashi's synthesis lacks chiral economy as all but one of the stereocenters in the starting material, D-mannitol, are discarded in the first few steps of the synthesis.

3.5.3.8 Magnus's Synthesis of the ABC rings of the Cortistatin Core

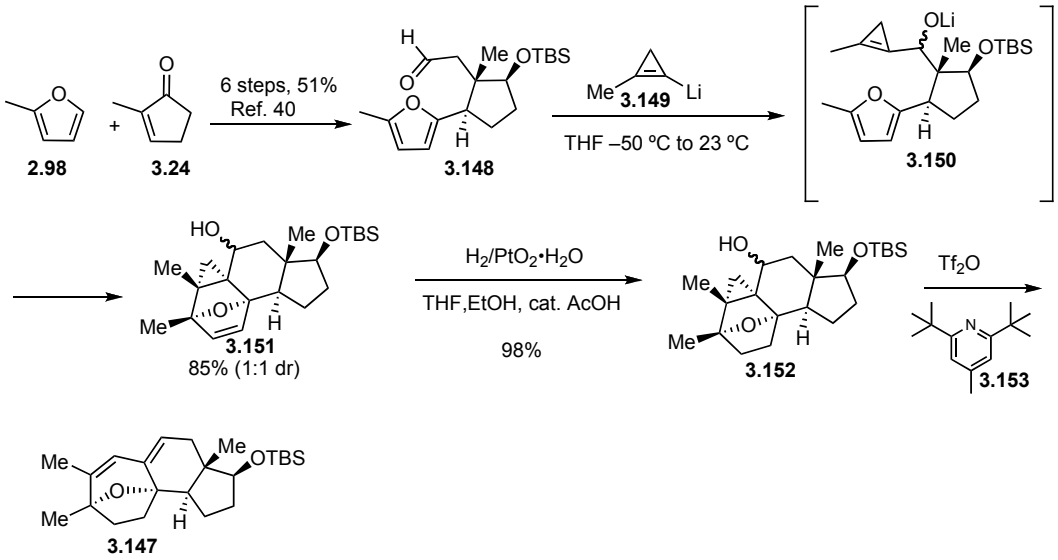
Magnus and coworkers reported a concise synthesis of the ABC rings of a racemic cortistatin A core. This synthesis proceeded in 30% overall yield from commercially available starting materials **3.24** and **2.98** (Scheme 3.29).[40]

Scheme 3.29



Key steps include addition of cyclopropenyllithium **3.149** to aldehyde **3.148** and a subsequent [4+2] intramolecular cycloaddition to form a mixture (1:1) of diasteromeric products. Following reduction of the oxabicyclic double bond to furnish **3.152**, both diasteromers were subjected to triflic anhydride and base, which catalyzed a cyclopropylcarbinyl rearrangement to afford **3.147** as a single diastereomer (Scheme 3.30).

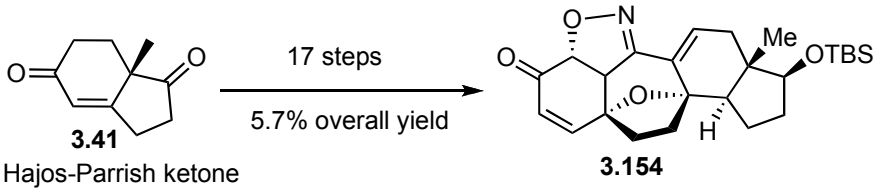
Scheme 3.30



3.5.3.9 Sorensen's Synthesis of the Cortistatin Core

The most recent approach to the cortistatin core was reported by Sorensen.[137] Starting from the Hajos-Parrish ketone **3.41**, Sorenson accessed advanced intermediate **3.154** in 17 steps and 5.7% overall yield (Scheme 3.31).

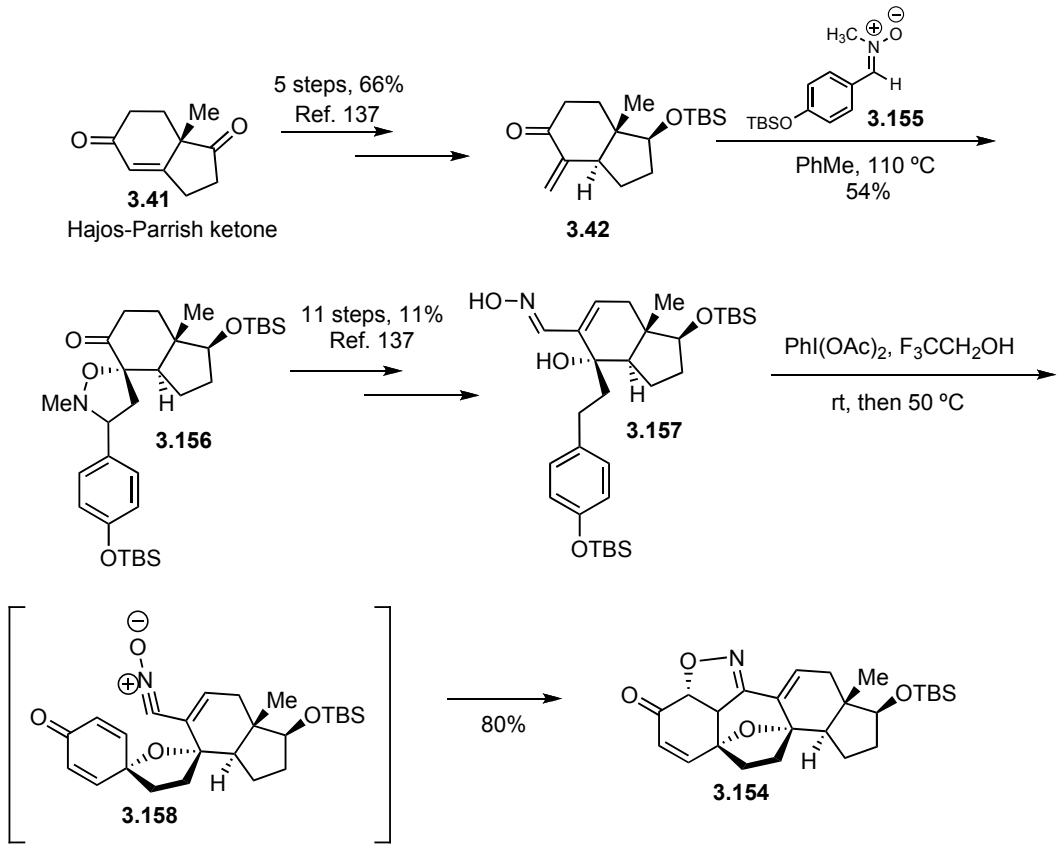
Scheme 3.31



Key steps include a [3+2] dipolar cycloaddition to produce **3.156** with perfect regio- and diastereoselectivity, and a hypervalent iodine-mediated oxidative cyclization to produce **3.154** (Scheme 3.32). Although a similar oxidative dearomatization was exploited in the syntheses by both Sarpong[127] and

Yang,[132] the concomitant oxidation of the aldoxime into a nitrile oxide, leading to a second ring closure, is both novel and noteworthy.

Scheme 3.32



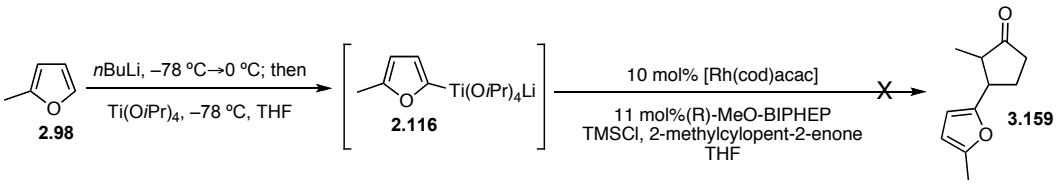
3.6 STUDIES TOWARD THE MARTIN GROUP APPROACH

3.6.1 Conjugate Additions Employing Furan-2-yl Nucleophiles

Having previously discovered conditions for enantioselectively adding a furan nucleophile to cyclopentenone (see chapter 2), we applied those conditions to the first key step of our cortistatin synthesis. Although we had previously used cyclopentenone as a substrate, our synthetic approach called for the use of 2-

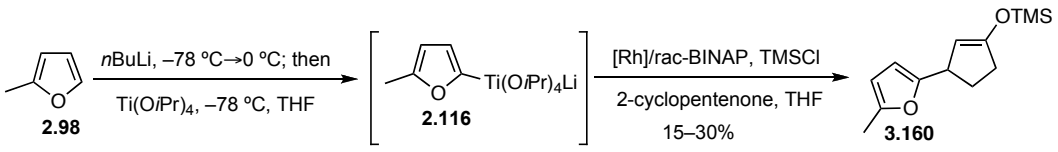
methylcyclopent-2-enone (**3.24**). However, in a model reaction with the furan-2-yltitanate **2.116**, none of the desired product was obtained (Scheme 3.33), illustrating that 2-methylcyclopentenone was incompatible with our methodology. This was not entirely surprising since there are virtually no examples of enantioselective conjugate additions with α-substituted Michael acceptors, likely due to steric buttressing between the α-substituent and the chiral rhodium species that precludes olefin insertion in the catalytic cycle.[138]

Scheme 3.33



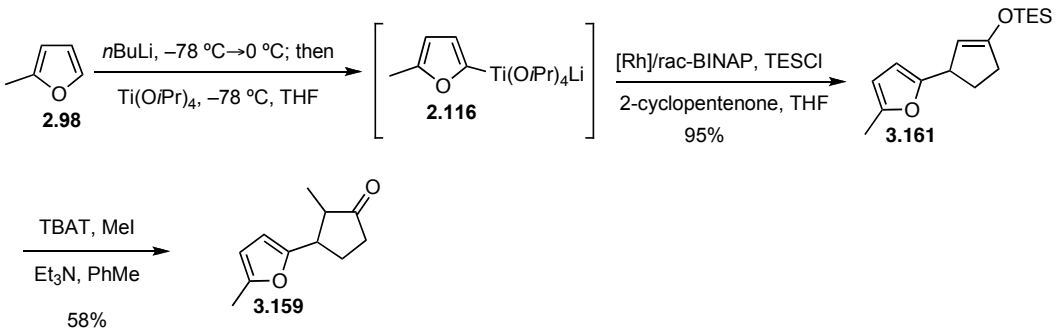
Fortunately, since our methodology employs non-aqueous conditions, it seemed plausible that the intermediate silyl enol ether could be isolated and the enolate generated therefrom trapped in a subsequent step with a methylating reagent. However, efforts to isolate the TMS enol ether **3.160** were fraught with difficulties. The TMS enol ether is very easily hydrolyzed, making workup difficult, and it cannot be purified via distillation nor with chromatography on alumina. As a consequence, **3.160** was consistently isolated in low yields (Scheme 3.34).

Scheme 3.34



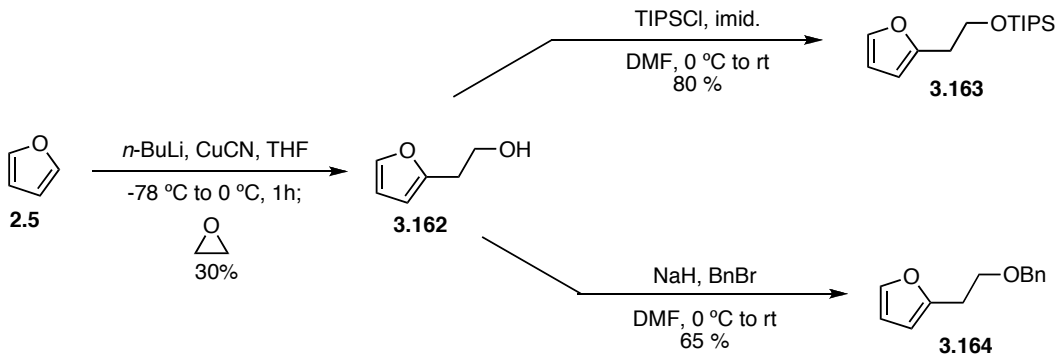
It was desirable to obtain a more stable silyl enol ether, but it was uknown if more hindered alkylchlorosilanes would effectively catalyze the reaction. Gratifyingly, chlorotriethylsilane was an effective Lewis acid catalyst in the conjugate addition, and the TES enol ether **3.161** was isolated in 95% yield (Scheme 3.35). The TES enol ether (**3.161**) was much easier to handle and could be purified via chromatography on neutral alumina. Additionally, this enol ether could be methylated in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) and iodomethane.

Scheme 3.35



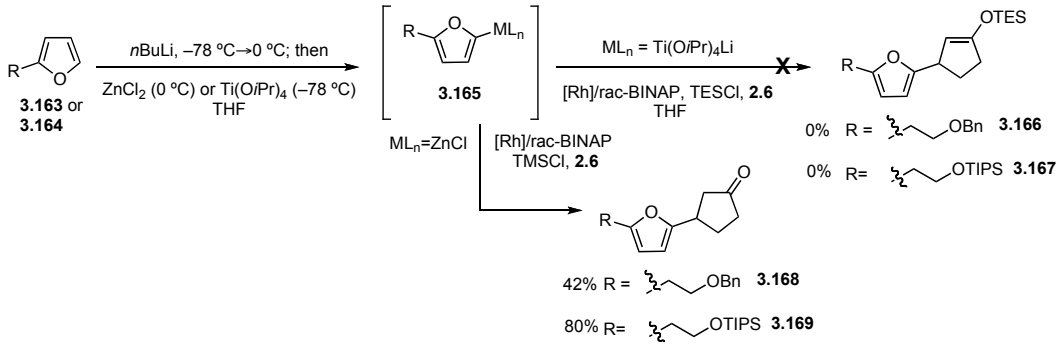
Satisfied with this result, we extended these conditions to other furan derivatives possessing side-chains that could be eventually transformed into a furylacetylaldehyde. Accordingly, furan compounds **3.163** and **3.164** were prepared by addition of a furanyl cuprate to ethylene oxide, followed by protection of the resultant alcohol **3.162** (Scheme 3.36).

Scheme 3.36



With these substituted furans in hand, the Rh-catalyzed conjugate addition was attempted in the presence of TESCl, but none of the TES enol ether product was formed (Scheme 3.37), nor was the hydrolyzed adduct isolated. This was unexpected as prior experiments using the analogous zinc chlorides had furnished the 1,4-adducts in good yield, but low ee.

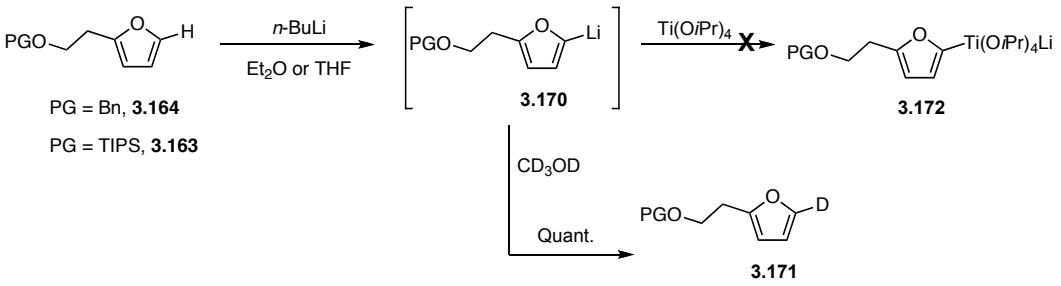
Scheme 3.37



Further investigation revealed that furan derivatives **3.163** and **3.164** may not have formed the necessary titanate (Scheme 3.38). Deuterium quench experiments confirmed that deprotonation was occurring quantitatively; however, iodine titration revealed that titanate formation had not occurred (Scheme 3.38). It

is unclear why iodine would fail to react with the resultant solution as it should contain either the aryllithium or the aryltitanate. It is possible that iodine is a poor titrant for some furyltitanates. For this reason the subsequent reaction was always attempted regardless of what the iodine titration results indicated.

Scheme 3.38

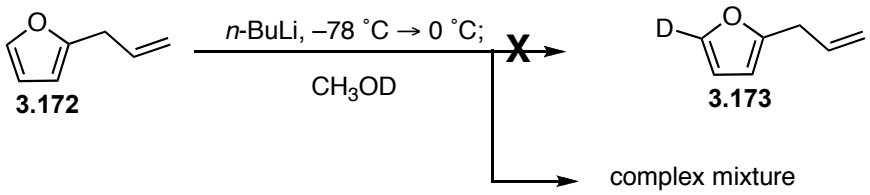


Although is not obvious why 2-methylfuran is compatible with titanate formation but **3.163** and **3.164** are not, our concurrent methodological studies on heteroaryl conjugate additions had revealed that titanate formation can sometimes be problematic. One such substrate that we had observed similar problems with was benzenesulfonylindole. In that case, we postulated that coordination of the sulfonyl oxygen to titanium may have resulted in an unreactive titanate species. In the present case, an analogous chelation may be occurring between titanium and the oxygen in the furan side chain.

In order to avoid furan derivatives with oxygenated side chains, addition reactions of 2-allylfuran and vinylfuran were evaluated. In the case of 2-allylfuran, the deprotonation step was troublesome (Scheme 3.39). Considering that the allylic hydrogens are weakly acidic, it is conceivable that non-selective deprotonation was occurring in the presence of *n*-BuLi, leading to a mixture of

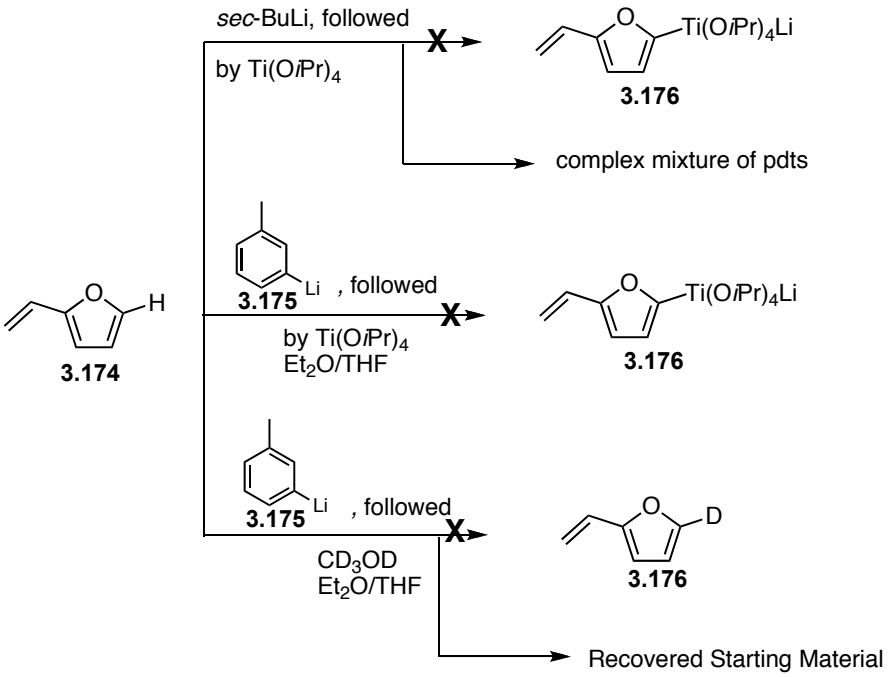
undesired products, perhaps via a ring-opening pathway. This hypothesis is supported by the lack of literature precedent for direct lithiation of 2-allylfuran at the C5 position.

Scheme 3.39



In the case of 2-vinylfuran, deprotonation with sec-BuLi also was not clean, leading to substantial decomposition (Scheme 3.40). It is known that *n*-BuLi will add into vinylfuran at the terminal alkene carbon and this type of side reaction may have been occurring with *sec*-BuLi. It has been reported that the use of *m*-tolyllithium as the base avoids that particular problem. [139] However, use of *m*-tolyllithium led only to recovery of starting material (Scheme 3.40). One possible explanation for these poor results may be that the vinylfuran is always contaminated with silanol by-products, an artifact of the preparation of vinylfuran, which involves acid-catalyzed elimination of trimethylsilanol from 1-(furan-2-yl)-2-(trimethylsilyl)ethanol.

Scheme 3.40

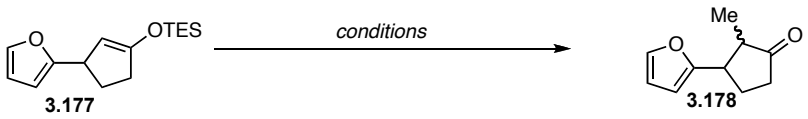


In light of these findings, it was decided to install the furan side chain at a later time. Thus, efforts were then focused on methylation of the TES enol ether.

3.6.2 Methylation of the TES Enol Ether

Of the numerous ways that have been reported to methylate enolates generated from silyl enol ethers, the most frequently used methods employ either a dry fluoride source or an alkylithium to generate the enolate, followed by subsequent addition of iodomethane. Variations on these two approaches were screened, with the best result deriving from the use of methyllithium as the nucleophile in the presence of hexamethylphosphoramide (HMPA) and $TiCl(O\textit{i}Pr)_3$ as additives (Table 3.1, entry 9). These rather unusual conditions were discovered in a footnote of a report by Noyori on enolate alkylations.[140]

Table 3.1



3.177 3.178

Entry	Conditions	Results
1	CsF, MeI, Et_3N in CH_3CN	**10%** (+ hydrolysis pdt and low mass recovery)
2	TBAT, MeI, Et_3N in DCM/PhMe [a]	**50%** (+ hydrolysis pdt)
3	TBAT, MeI, Hunig's base in DCM/PhMe	**24%** (hydrolysis pdt is major pdt)
4	TBAT, MeI, NaH in DCM/PhMe	**68%** (hydrolysis pdt is minor pdt)
5	MeI, NaH in DCM/PhMe (24 h)	Unreacted Starting Material
6	MeI, NaH in DCM/PhMe (>3 d)	**22% (**1:1 mixture of hydrolysis and desired pdt)
7	MeLi, MeI in THF (0 ˚C)	**50%** (mixture of desired and polyalkylated pdts)
8	MeI, MeLi, HMPA in THF (–78 ˚C)	**24%** mixture of desired and polyalkylated pdt
9	MeI, MeLi, HMPA, $TiCl(OiPr)_3$ in THF (–78 ˚C)	**67%** (only one diastereomer isolated)

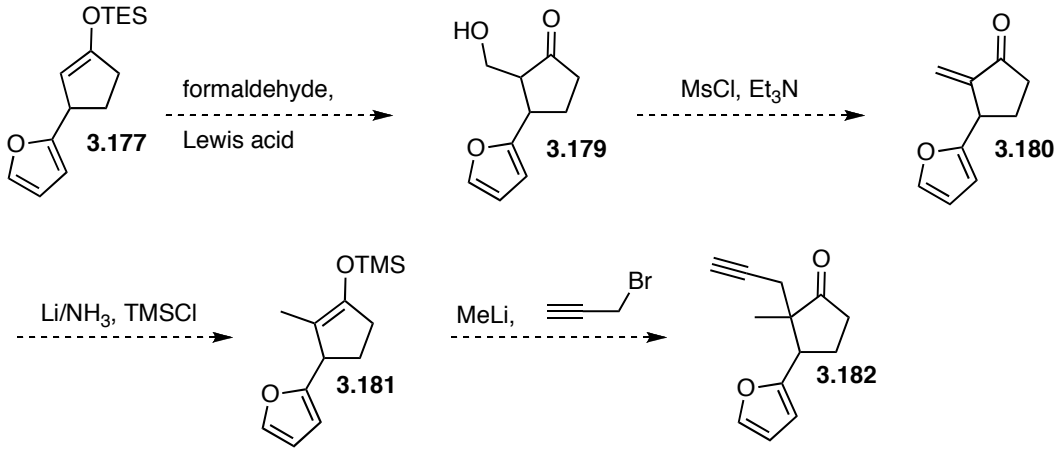
[a] slow addition of TES enol ether and Et_3N to the solution of TBAT via syringe pump (0.1 mL/1 h)

Unfortunately, when these reaction conditions were scaled up from a 50 milligram scale to a multi-gram scale, the yields plummeted to the 30% to 50% range. Due to these problems, efforts were focused on an alternative synthetic route.

It was envisioned that TES enol ether **3.177** could participate in a Mukaiyama-aldol reaction to form **3.179** that, when subjected to MsCl and

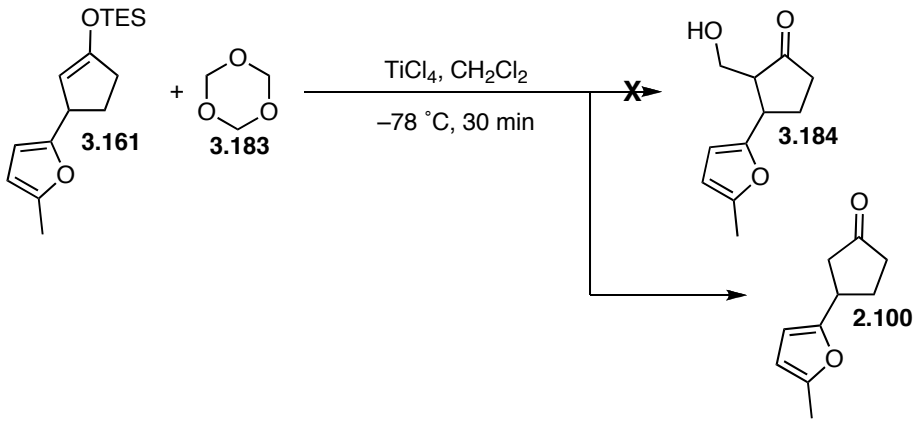
triethylamine, could undergo an elimination to form exocyclic alkene **3.180**. Reduction of this enone using Li/NH_3 could lead to the desired TMS enol ether **3.181**, which could be propargylated to form **3.182** (Scheme 3.41).

Scheme 3.41



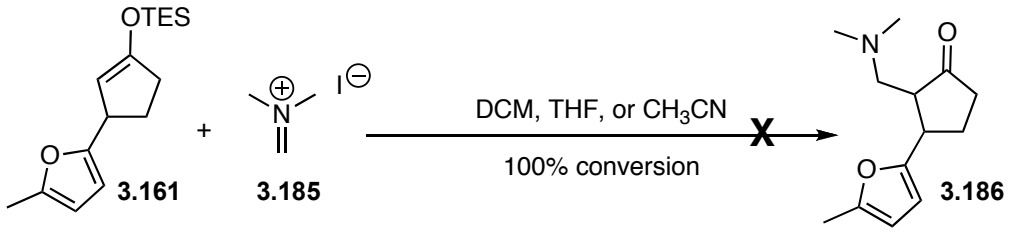
The first step of the newly devised synthetic strategy was attempted using 1,3,5-trioxane as the formaldehyde source and $TiCl_4$ as the Lewis acid catalyst.[141] However, the major product isolated was the hydrolyzed silyl enol ether (Scheme 3.42).

Scheme 3.42



As formaldehyde sources are notoriously difficult to work with and difficult to dry thoroughly, a condensation reaction was performed with Eschenmoser's salt (Scheme 3.43). Although the starting material was completely consumed, a complex mixture of compounds was isolated that included neither the desired product **3.186** nor the hydrolysis product **2.100**.

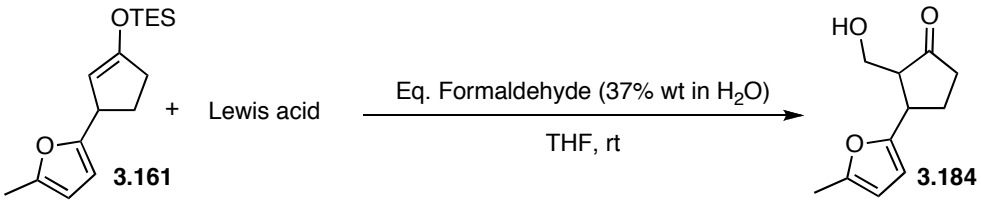
Scheme 3.43



Kobayashi has reported the use of lanthanide triflates to catalyze aldol reactions with aqueous formaldehyde and TMS enol ether ethers.[142] Based upon these results, a variety of lanthanide Lewis acids were tested, and a moderate yield of the desired product **3.184** could be obtained in 44% yield (Table 3.2,

entries 4 and 5). The majority of the mass balance, however, was still the undesired hydrolysis product.

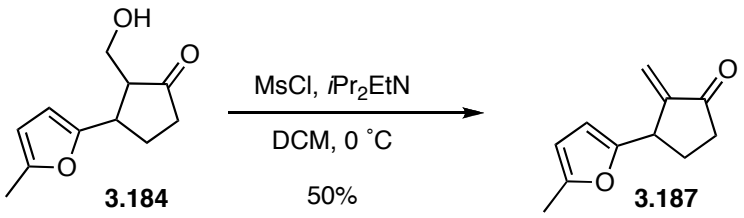
Table 3.2



Entry	Lewis acid	Time(h)	Equivalents of Formaldehyde	Yield(%)	Conversion(%)
1	$Yb(OTf)_3$	24	25	22	100
2	$Y(OTf)_3$	24	25	22	100
3	$Sc(OTf)_3$	96	25	0	100
4	$Sm(OTf)_3$	24	25	44	100
5	$La(OTf)_3$	96	25	44	100
6	$Yb(OTf)_3$	24	17	22	100
7	$Sm(OTf)_3$	24	17	29	100

The aldol product **3.184** was moved forward and successfully converted into enone **3.187** in one pot (Scheme 3.44) using conditions reported by Magnus.[143] The product was not carried on further as it was a model substrate and cannot be transformed into the target compound **3.182**. However, it did establish proof of principle for the first two steps in the strategy outlined in Scheme 3.41.

Scheme 3.44

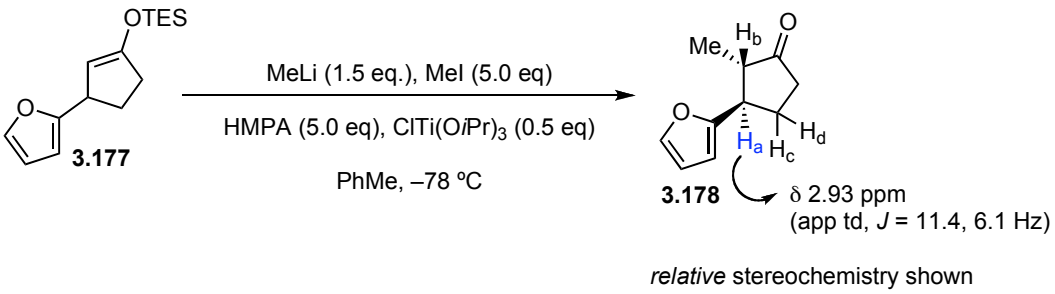


Concurrent with exploring the alternative strategy described above, further efforts were made to optimize the conditions for large-scale methylation of the TES enol ether. The effects of solvent, equivalents of methyllithium, and additives were examined. It was observed that the rate of enolate formation varied greatly with solvent. In toluene, enolate formation was quite slow and required the addition of HMPA to go to completion. In THF the enolate formed without the addition of additives and in diethyl ether the enolate did not form to any significant extent, even in the presence of additives.

In addition to optimizing these variables, it occurred to us that a possible obstacle for the methylation reaction could be the triethylsilanol impurity that co-elutes with **3.177** during chromatography on alumina. Triethylsilanol is produced during the workup following the conjugate addition reaction and is difficult to remove without hydrolyzing **3.177**. Gratifyingly, it was found that the majority of this silanol could be removed via kugelrohr distillation, under vacuum, without destroying the TES enol ether in the process. This purification, in conjunction with the use of toluene as a solvent and HMPA as the additive provided the best result to date. In the event, one major diastereomer was isolated in 70% yield, indicated in the ^{1}H NMR spectrum by the presence of only one doublet at 1.13 ppm, which corresponded to the methyl group (Scheme 3.45). These results were

reproducible on multi-gram scale. The relative stereochemistry was assigned to be *trans* based upon the spectral data for proton Ha, which had an apparent td splitting pattern with coupling constants of 11.4 and 6.1 Hz. H_a is coupling to protons H_b, H_c, and H_d and will exhibit the largest coupling with those protons that are trans to it. Since two of the three couplings are large, it is reasonable to conclude that two of the three coupled protons are trans to H_a, which would obviously require that H_b be trans to H_a since both H_c and H_d cannot both simultaneously be trans to H_a.

Scheme 3.45



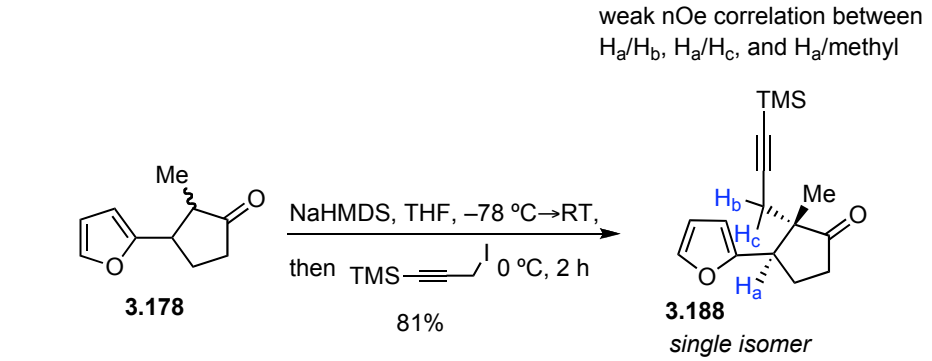
3.6.3 Propargylation and Side-Chain Installation

The propargylation of **3.178** was predicted to be nontrivial due to the question of regioselectivity, as well as the fact that quaternary carbons are difficult to create. Initially, the soundest approach appeared to be to make the more substituted TMS sily enol ether first and then propargylate it in a second step. However, all attempts to prepare this sily enol elther met with failure. Thus, efforts were focused instead on direct propargylation.

A variety of solvents, bases and propargyl sources were screened. The use of propargyl bromides **3.189** and **3.191** did not furnish any of the desired product,

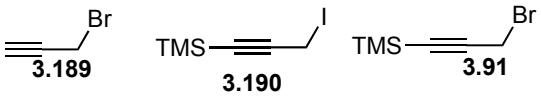
with only recovered starting material being recovered in a low mass balance. The use of HMPA and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) resulted in slightly decreased yields of product. A profound solvent effect was observed, with toluene and THF consistently furnishing the best yields and dioxane and DMSO furnishing the lowest yields. The reaction time was crucial, with times longer than 2 h resulting in diminished yields. Optimal results were obtained using NaHMDS (0.9 equivalents) and TMS-protected propargyl iodide **3.190** in THF in the presence of a slight excess of the ketone. It was crucial that the propargyl iodide **3.190** be prepared immediately prior to use and kept in the dark. The reaction proved to be extremely regio- and stereoselective, furnishing only one diastereomer in 81% yield (Scheme 3.46). nOe studies did not elucidate which diastereomer was formed because weak nOe correlations were found between Ha and methyl group, as well as between H_a and the protons on the propargylic carbon, H_b and H_c. Derivatization of **3.188** to its phenyl hydrazone did not produce a solid.

Scheme 3.46



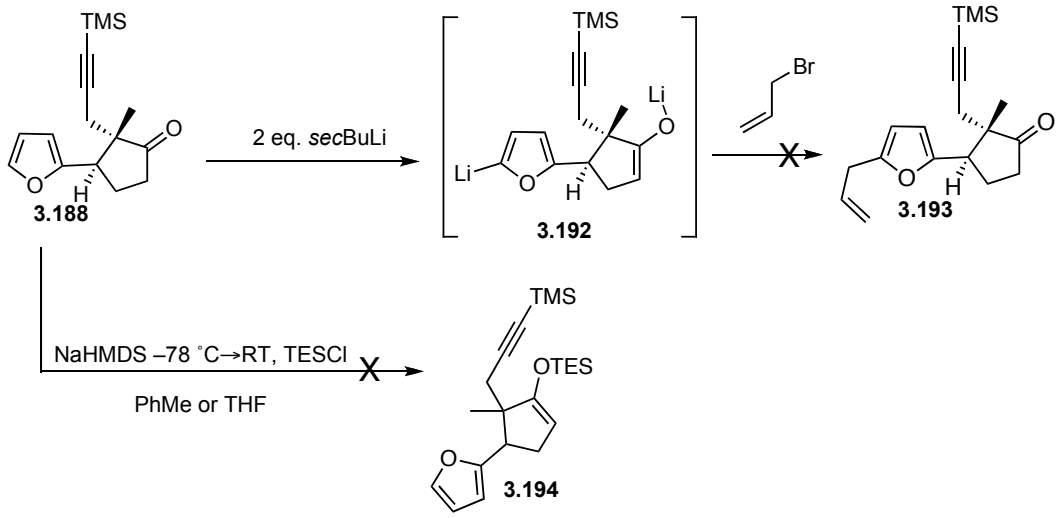
Solvents screened: PhMe, Et_2O, DMSO, THF, dioxane, PhH
Additives screened: HMPA, DMPU

Propargyl electrophiles screened:



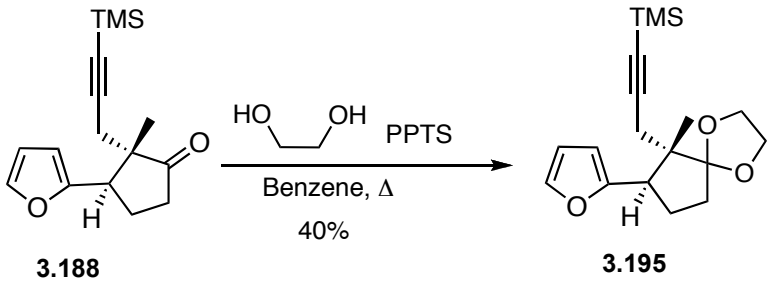
With **3.188** in hand, functionalization at C5 of the furan ring was attempted (Scheme 3.47). In an effort to avoid two separate steps, the formation of intermediate dianion **3.192** was attempted using excess *sec*-BuLi, followed by addition of allyl bromide. In the reaction, a solution of furan **3.188** was prepared in THF and two equivalents of *sec*-BuLi were added dropwise at –78 ˚C. The resultant solution was warmed to 0 ˚C for 90 min, and then allyl bromide was added at –78 ˚C. None of the desired product **3.193** was obtained, nor was starting material recovered. Attempts to isolate the TES enol ether **3.194** also failed and furnished a low mass balance of starting material (Scheme 3.47).

Scheme 3.47



Protection of the neopentyl ketone as its 1,3-dioxolane was attempted in the presence of ethylene glycol and pyridinium *para*-toluenesulfonate in refluxing benzene, with the aid of a Dean-Stark apparatus, but this reaction was low yielding, likely due to the steric hindrance presented by the adjacent quaternary carbon (Scheme 3.48).

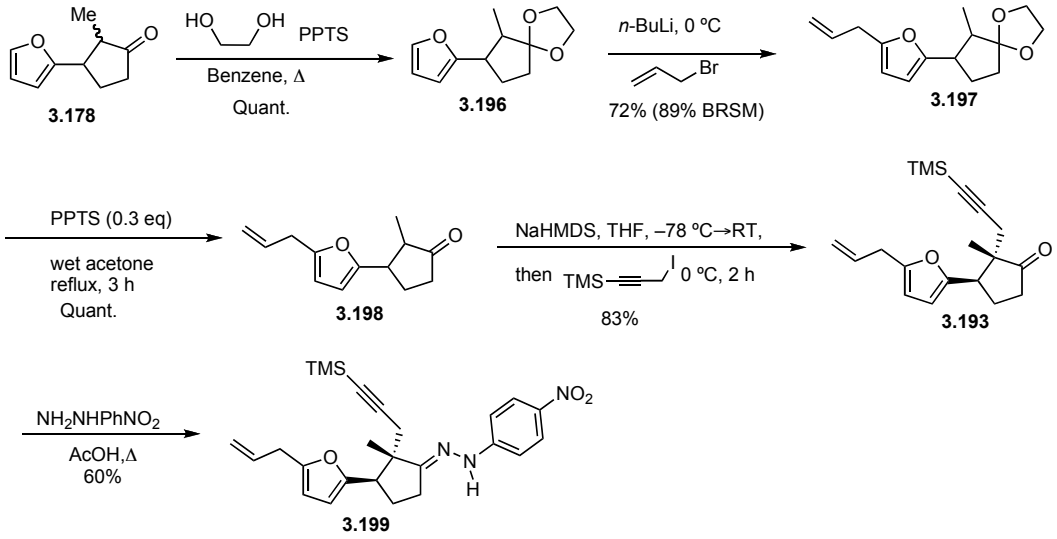
Scheme 3.48



The order of the synthetic sequence was altered so that the protection of the ketone would precede propargylation. Towards that end, **3.178** was protected as its ketal in quantitative yield. Subsequent allylation of the furan ring proceeded

smoothly to give **3.197** in 72% yield (89% BRSM), and deprotection of the ketone occurred in quantitative yield to furnish **3.198**. Propargylation of **3.198** using the optimized conditions for **3.178** provided the desired product **3.193** in 83% yield as one major diastereomer (Scheme 3.49). Attempts to isolate a crystal via formation of the *p*-nitrohydrazone and phenylhydrazone derivatives were unsuccessful because both products were oils.

Scheme 3.49



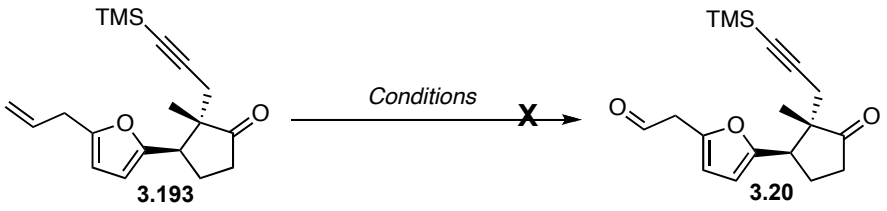
Although it was necessary to introduce two protection/deprotection steps in order to functionalize the furan at C5, there was no loss in overall yield due to the excellent conversion in both of those steps.

3.6.4 Functionalization of the Furan Side Chain

In order to convert the allyl side chain of **3.193** to the requisite arylacetylaldehyde **3.20**, a one-step oxidative cleavage was attempted. Ozonolysis of **3.193** followed by reduction of the intermediate ozonide led to a low mass

balance of a complex mixture of products (Table 3.3, entry 1). It is well-known that furan can participate in [4+3] and [3+2] cycloadditions with ozone, furnishing unstable adducts that readily undergo ring opening.[144] If the furan ring reacted preferentially with ozone over the terminal double bond, a variety of unwanted oxidation products could potentially be formed, many of which would be polar enough to be lost in the aqueous phase during workup. Oxidation of **3.193** under Johnson-Lemieux reaction conditions also led to low mass recovery of a complex mixture of products (Table 3.3, entry 2). Interestingly, other reported efforts to perform Johnson-Lemieux reactions on similar compounds have also failed to furnish the desired aldehydes.[145] Submission of **3.193** to potassium permanganate and tetrabutylammonium chloride in DCM,[146] also known as "purple DCM," resulted only in recovered starting material (Table 3.3, entry 3).

Table 3.3

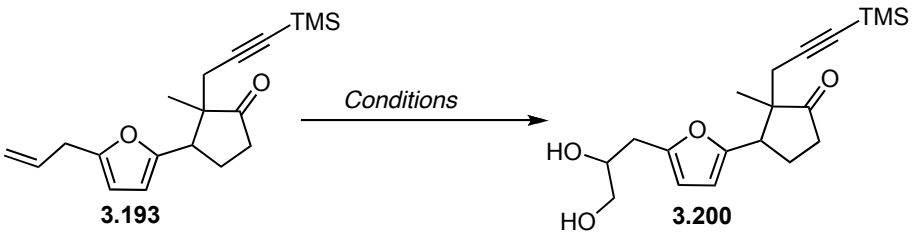


3.193 **3.20**

Entry	Conditions	Results
1	i. O_3, MeOH, –78 ºC (5 min) ii. DMS	Low mass recovery, complex mixture
2	OsO_4, $NaIO_4$	Low mass recovery, complex mixture
3	$KMNO_4$,TBACl, DCM; AcOH/NaOAc buffer workup (pH=3.7)	Recovered starting material only

A two-step oxidation involving dihydroxylation of the olefin to the diol and subsequent cleavage was also investigated. The use of potassium osmate(VI) dihydrate and *N*-methylmorpholine-*N*-oxide (NMO) as the oxidant provided the desired diol in low yield. Reacting **3.193** with commercially available asymmetric dihydroxylation reagent (ADMix-α) led to a moderate 56% yield of **3.200**. Despite the observation that methanesulfonamide slows the dihydroxylation of mono-substituted olefins,[147] the use of methanesulfonamide was necessary to achieve moderate conversion. The absence of this additive led to isolation of only starting material. Literature precedent involving the dihydroxylation of vinyl furan indicates that very long reaction times (96 h) are necessary to achieve high yields.[148] In light of this, prolonged reaction times may be necessary improve the conversion of the starting material to the product.

Table 3.4

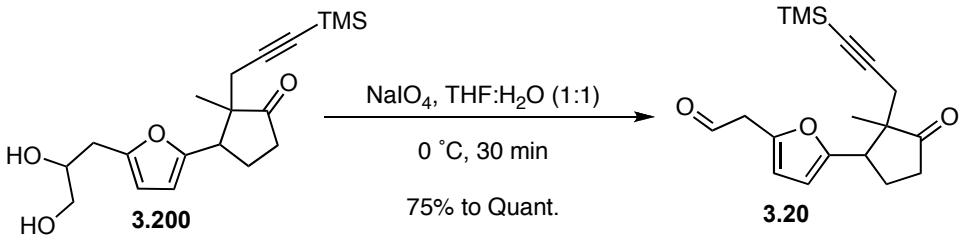


Entry	Conditions	Results
1	AD-Mixα , t-BuOH/H_2O (1:1) $CH_3SO_2NH_2$, RT, 16 h	56% yield, 80% BRSM
2	$K_2OsO_4(2H_2O)$, NMO Acetone:H_2O (1:1), 18 h	37% yield, 70% BRSM

Subsequent oxidative cleavage of diol **3.200** occurred smoothly in the presence of sodium periodate to yield the desired furylacetylaldehyde **3.20** in 75-

100% yields (Scheme 3.50). Purification of this material on silica gel led to decomposition and low recovery of the desired aldehyde. Therefore, in most cases the aldehyde was carried forward without purification.

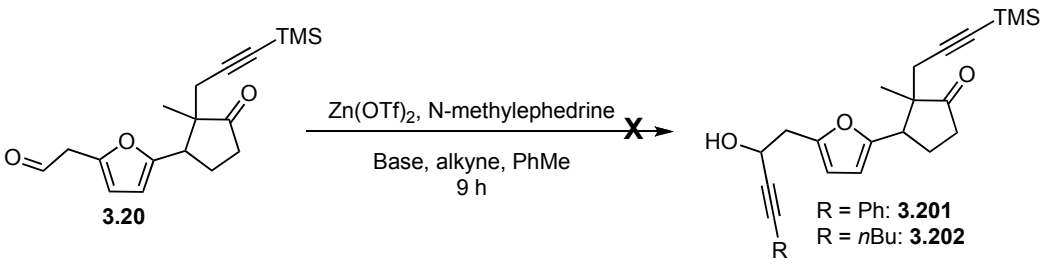
Scheme 3.50



3.6.5 Diastereoselective Alkynylation

With aldehyde **3.20** in hand, an asymmetric alkynylation was attempted using conditions reported by Carriera.[118] In the presence of both triethylamine and Hunig's base, the aldehyde was completely consumed, but the desired product was not isolated (Table 3.5). Using different alkynes, e.g., phenylacetylene and 1-hexyne, did not appear to affect the reaction. Drying zinc triflate thoroughly under vacuum immediately prior to use did not affect the reaction. Similarly, distillation of the alkynes immediately prior to use did not improve the reaction. Although Carreira has reported that this chemistry is not very sensitive to air, the reaction was also performed under argon, but that did not alter the outcome. Monitoring of the reaction via TLC analysis revealed multiple spots throughout the course of the reaction.

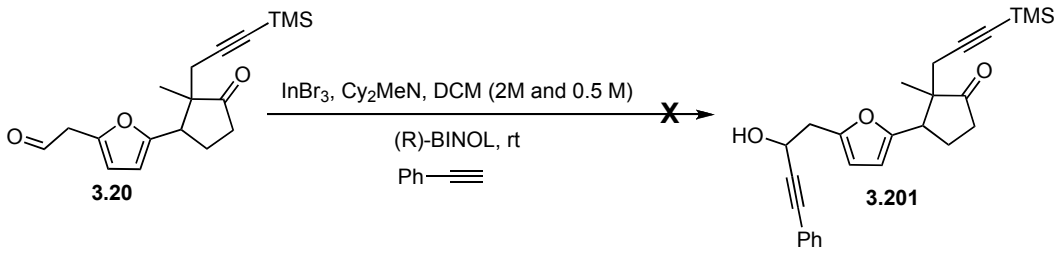
Table 3.5



Entry	Base	Alkyne	Results
1	Et_3N	Ph—	Aldehyde consumed; complex mixture isolated
2	iPr_2EtN	Ph—	Aldehyde consumed; complex mixture isolated
3	Et_3N	nBu—	Aldehyde consumed; complex mixture isolated
4	iPr_2EtN	nBu—	Aldehyde consumed; complex mixture isolated

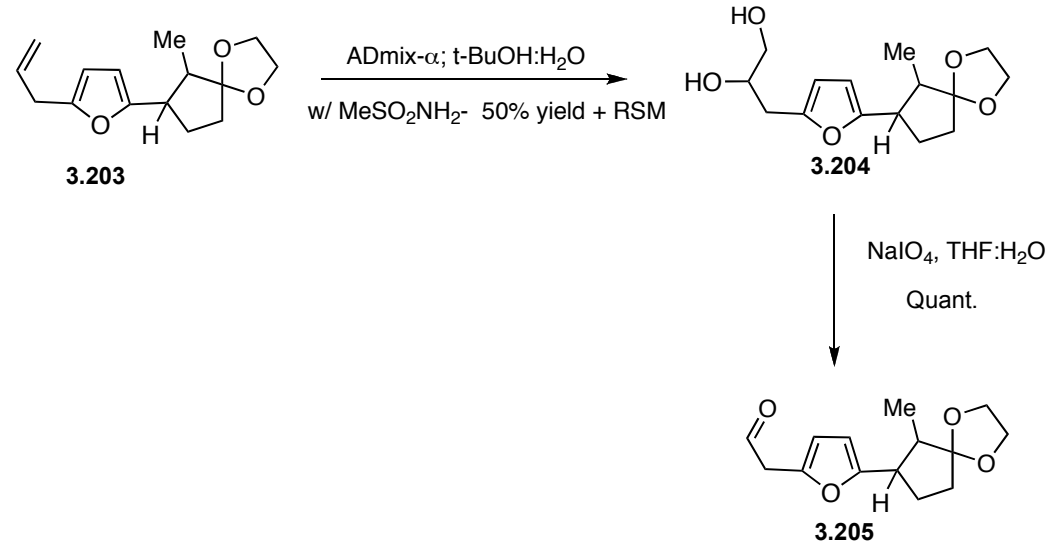
Although Carreira's work in this area is certainly the most well-developed and commonly used, there are other methods for effecting the asymmetric addition of alkynes to aldehydes. Shibasaki has reported a method employing indium bromide and (*R*)-BINOL to add phenylacetylene to a variety of aldehydes in good yield and high enantiomeric excess.[149] However, when these conditions were applied to aldehyde **3.20**, the desired product was not obtained and a complex mixture of compounds was again isolated (Scheme 3.51).

Scheme 3.51



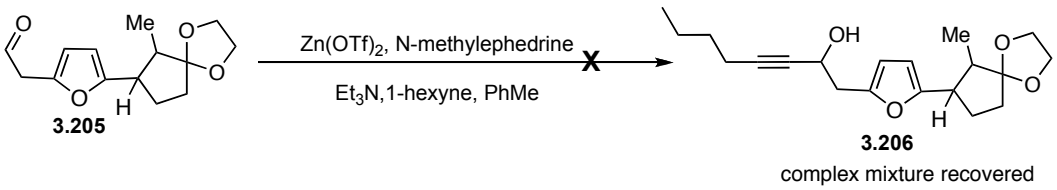
It is known that arylacetylaldehydes can be problematic to work with due to their propensity to enolize and undergo self-condensation. In order to minimize deleterious self-condensation reactions, the modified aldehyde **3.205** was prepared, in which the ketone is protected (Scheme 3.52). Although it is sterically hindered, the ketone could be a potential aldol partner and may be contributing to this substrate's instabiity.

Scheme 3.52



Upon submission of **3.205** to Carreira's conditions, this substrate proved to also be incompatible with alkynylation (Scheme 3.53).

Scheme 3.53



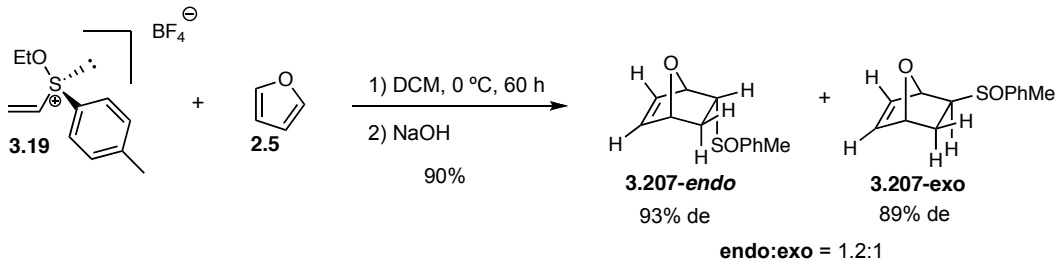
Pu has also reported a method for enantioselective acetilide addition to aldehydes, but unfortunately it necessitates the use of a glovebox.[150] Future trials may be successful using a slow addition of the aldehyde with the conditions reported by Carreira. Due to the high reaction concentration required with Carreira's method (2 M in DCM), it would be necessary to peform this reaction on a reasonable scale.

Thus, the use of a diastereoselective alkynlation may not be feasible with furylacetyl aldehyde **3.20**. However, it would be worthwhile to try this reaction on larger scale, using a very slow addition.

3.6.6 Diels-Alder Key Step

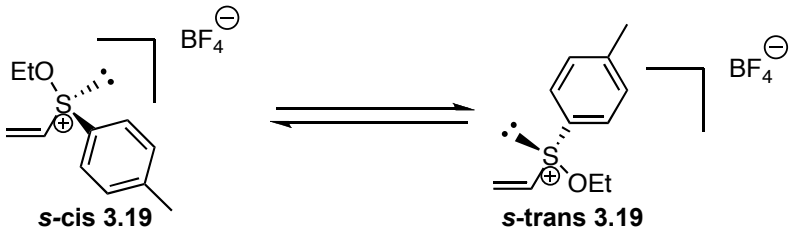
Early in our investigations, we probed the feasibility of an intermolecular Diels-Alder reaction. Our approach was based upon Kagan's reports that furan and chiral vinylsufonium salt **3.19** produced Diels-Alder adducts in high yields and diastereomeric excess (Scheme 3.54).[107]

Scheme 3.54



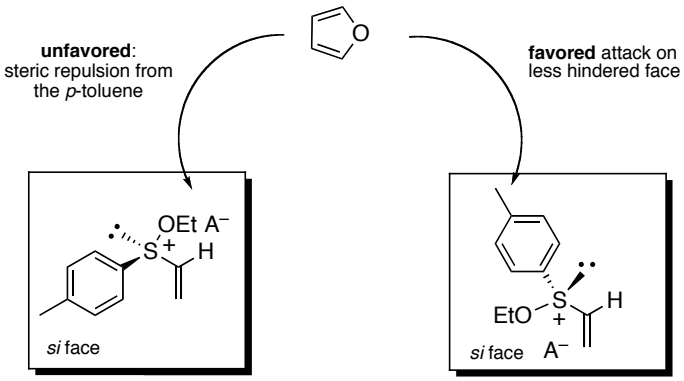
Diastereoselectivity in this reaction is contingent upon two things: conformational selectivity of the dienophile and facial selectivity in the Diels-Alder transition state. In the context of conformational preferences of the dienophile, it is known that vinyl sulfoxides can exist in either the *s*-cis or *s*-trans conformation (Figure 3.7).[151, 152]

Figure 3.7



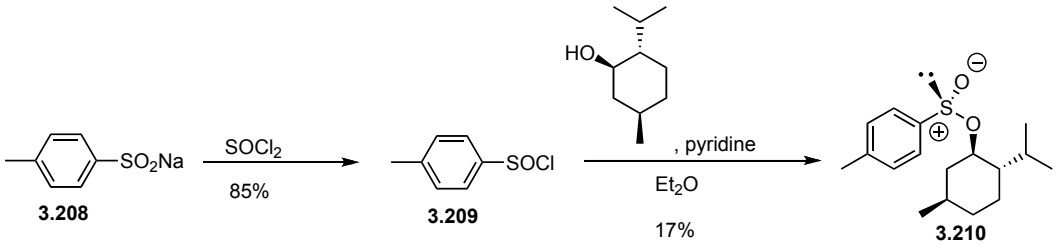
Kagain has stated, without explanation, that approach from *si* face of the sulfoxide is the preferred pathway. Kagan postulated that the s-cis conformer is preferred in the Diels-Alder transition state as it allows the most sterically accessible approach to the *si* face of the sulfoxide, away from the bulky *p*-tolyl group (Figure 3.8).

Figure 3.8



We investigated the application of Kagan's reaction conditions to our Diels-Alder key step. It was first necessary to synthesize the chiral dienophile **3.19**, which proved much more difficult than anticipated. The synthesis involves a four-step sequence starting from the sodium salt of *p*-toluenesulfinic acid. The first two steps include the formation of *p*-tolylsulfinylchloride, followed by displacement of chloride ion with (–)-menthol (Scheme 3.55). The product **3.210** was isolated via recrystallization in consistently poor yields, most likely due to inferior recrystallization conditions.

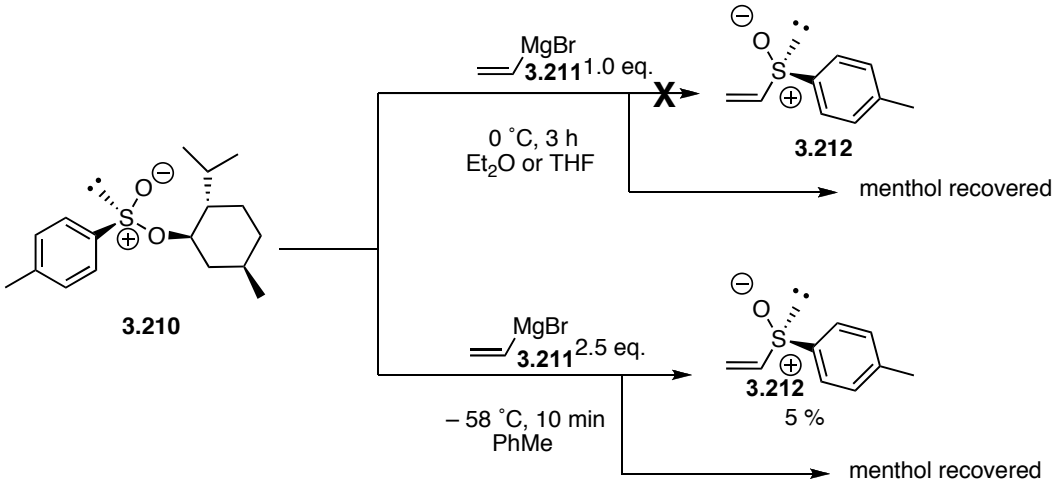
Scheme 3.55



The third step of the sequence involved the reaction of a vinyl Grignard reagent with **3.210** to furnish the optically active vinylsulfoxide **3.212**. The literature conditions reported for the generation of **3.212** are very diverse, ranging

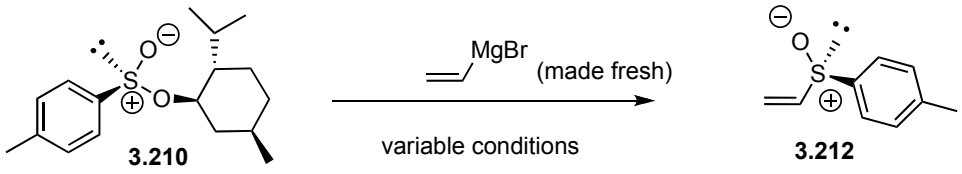
from 10 minutes at –58 ˚C in toluene to reflux for 3 h in diethyl ether.[153, 154] All attempts to reproduce the results from those literature procedures failed and menthol was recovered in quantitative yield (Scheme 3.56).

Scheme 3.56



After screening a number of conditions, we found that a 64 % yield of the desired sulfoxide **3.212** could be obtained in benzene at room temperature in the presence of 1.3 eq. of the vinyl Grignard reagent. It was critical to keep the Grignard reagent within a strict stoichiometric range, and to prepare the Grignard reagent immediately prior to use (Table 3.6).

Table 3.6



3.210 **3.212**

Entry	Solvent	Temperature	Grignard Equivalents	Yield(%)
1	Benzene	23 ºC	2.5	<5
2	THF	–58 ºC	2.5	<5
3	Et_2O	–58 ºC	2.5	<5
4	THF	–58 ºC	1.5	5
5	Benzene	23 ºC	1.5	53
6	Benzene	23 ºC	1.3	64
7	Benzene	23 ºC	1.0	50

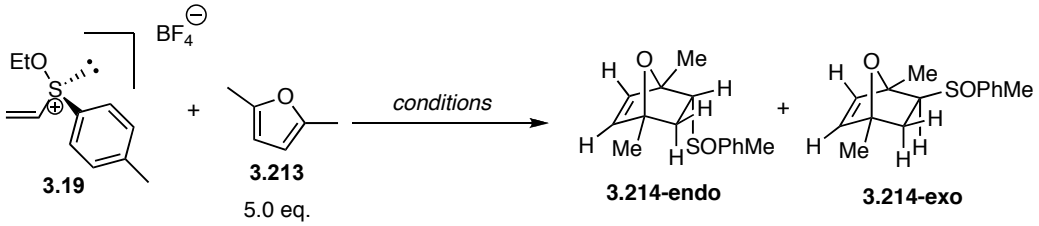
The final step of the synthesis of the dienophile **3.212** was a straightforward alkylation of the sulfoxide with Meerwein's reagent (Scheme 3.57). The desired product **3.19** was isolated easily and used without purification in the Diels-Alder reactions of interest.

Scheme 3.57

3.212 **3.19**

In an effort to simplify the analysis of the reaction, the asymmetric Diels-Alder step was first attempted with the model substrate dimethylfuran (**3.213**). By using dimethylfuran, the total number of possible diastereomers would be minimized to four, and the issue of regioisomers would be eliminated completely. To our delight, the formation of *endo*-**3.214** and *exo*-**3.214** was achieved in 73% yield and 77% and 82% diastereomic excess, respectively. The best results were achieved when the reaction was conducted in chloroform at –20 ˚C (Table 3.7, entry 5). The diastereomeric excess was determined by ^{1}H NMR integration of the proton alpha to the sulfoxide moiety. Four distinct chemical shifts are observed for that proton in the ^{1}H NMR, corresponding to the four diastereomers.

Table 3.7

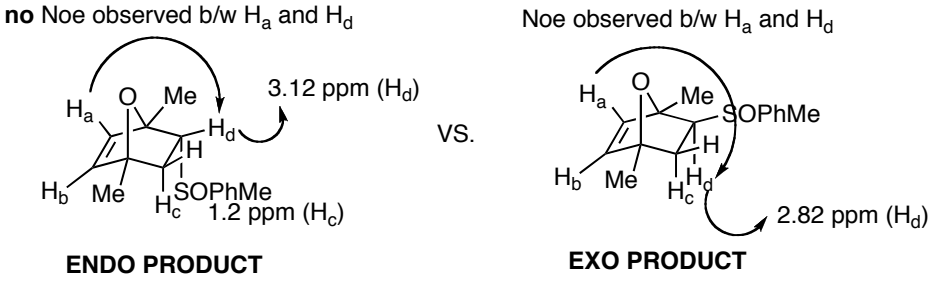


Entry	Conditions	Yield(%)	Endo/Exo Ratio	Endo de (%)	Exo de (%)
1	DCM, rt, 2.5h	70	2:1	50	62
2	DCM, 0 ºC, 36h	95	1.6:1	60	66
3	$CHCl_3$, 0 ºC, 36h	86	1.6:1	60	68
4	DCM, –20 ºC, 2.5 h	0	n/a	n/a	n/a
5	$CHCl_3$, –20 ºC, 36h	73	2:1	77	82

n/a = not applicable

The endo/exo ratios we observed were in agreement with those that Kagan observed when reacting **3.19** with furan.[6] Endo/exo assignments were based upon nOe correlations between the vinyl proton and the pseudo-axial proton alpha to the sulfoxide moiety (Figure 3.9). The exo products exhibited an nOe correlation between H_d and H_a, whereas the endo products did not.

Figure 3.9



Confirmation of the structures of the Diels-Alder adducts was obtained by Noah Benjamin, who obtained crystal structures of both the major endo and major exo adducts. The major endo product is shown in Figure 3.10 and the major exo product is shown in Figure 3.11.

Figure 3.10: Endo Main

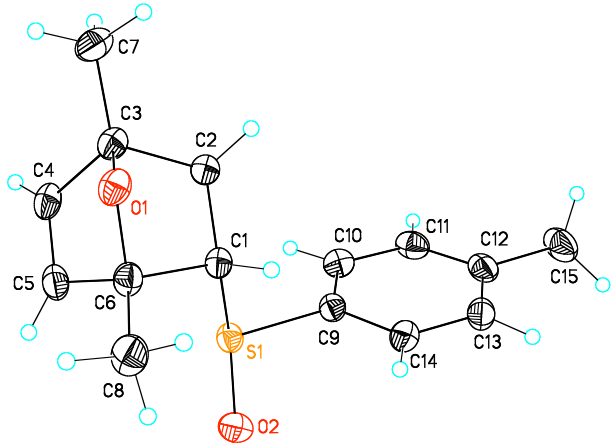
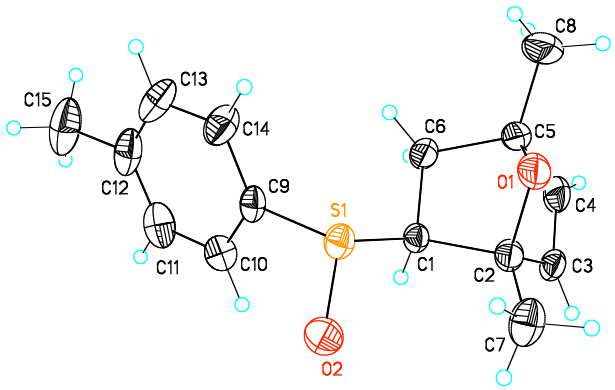


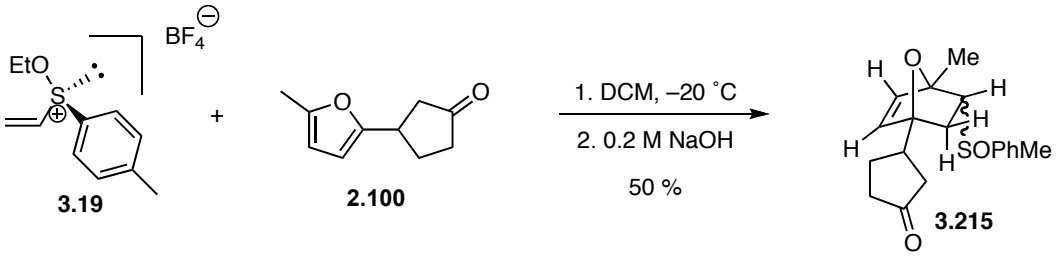
Figure 3.11: Exo Main



With the successful extension of Kagan's Diels-Alder chemistry to 2,5-disubstituted furans, we tried the reaction with the more complex substrate **2.100** (Scheme 3.58). Compound **2.100** was employed in racemic form because at the time this experiment was performed we had not yet established conditions for the

enantioselective conjugate addition of furan to cyclopentenone. When **2.100** was submitted to the asymmetric Diels-Alder reaction two major products were obtained. A total of 16 possible diastereomers can be produced by the reaction of racemic **2.100** with the chiral dienophile **3.19**. Although the NMR evidence is not conclusive due to overlapping signals in the proton spectrum, it is consistent with an oxabicycle such as **3.215** due to the presence of vinyl protons at 6.50 ppm and 6.33 ppm in the ^{1}H NMR spectrum, which is similar to the oxabicyclic compound **3.214.** Additionally, ^{1}H NMR spectrum shows the disappearance of the furan protons at 5.92 ppm and 5.86 ppm from the starting material, as well as the presence of a new tolyl group. It was not discernible by NMR whether the two major products differ only at the stereochemistry at the cyclopentanone, or if they are endo/exo- or regioisomers. Better assignments would require the separation of the individual products from the mixture.

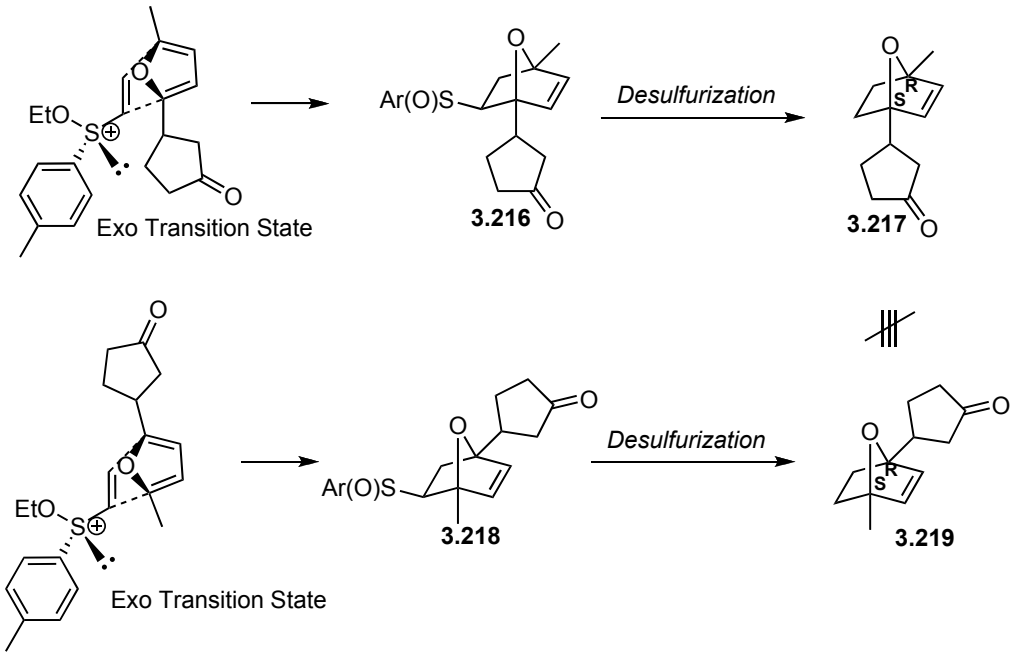
Scheme 3.58



This example raises the issue of regioselectivity. In addition to the possibility of forming endo/exo isomers, there is the further complication of forming regioisomers, leading to an increased number of products. Even if the reaction proceeds with exo selectivity, regiosisomers can lead to different

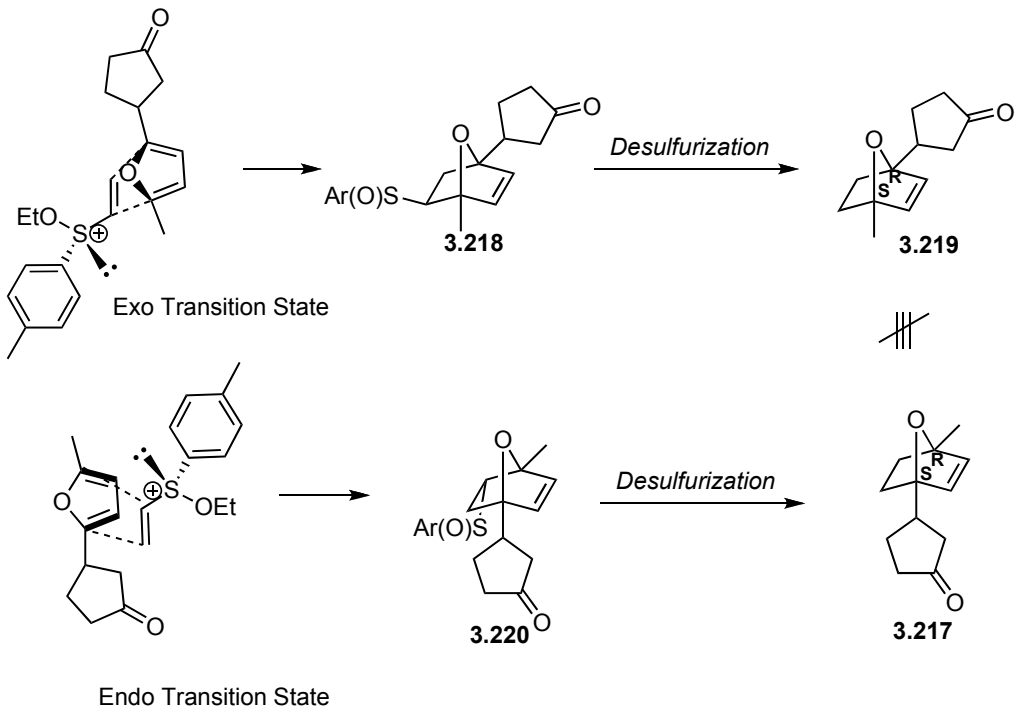
enantiomers following desulfurization (Figure 3.12). The same analysis with an endo-selective reaction leads to the same conclusions.

Figure 3.12



Similar problems arise in terms of endo/exo selectivity (Figure 3.13). Even if regioselectivity is high, endo/exo isomers can lead to different enantiomers following desulfurization. Thus, in order to achieve excellent enantiomeric excess of the desulfurized Diels-Alder adducts, the reaction must also exhibit endo/exo- and regioselectivity as well. Kagan's method suffers from low endo/exo selectivity, and regioselectivity was not examined.

Figure 3.13



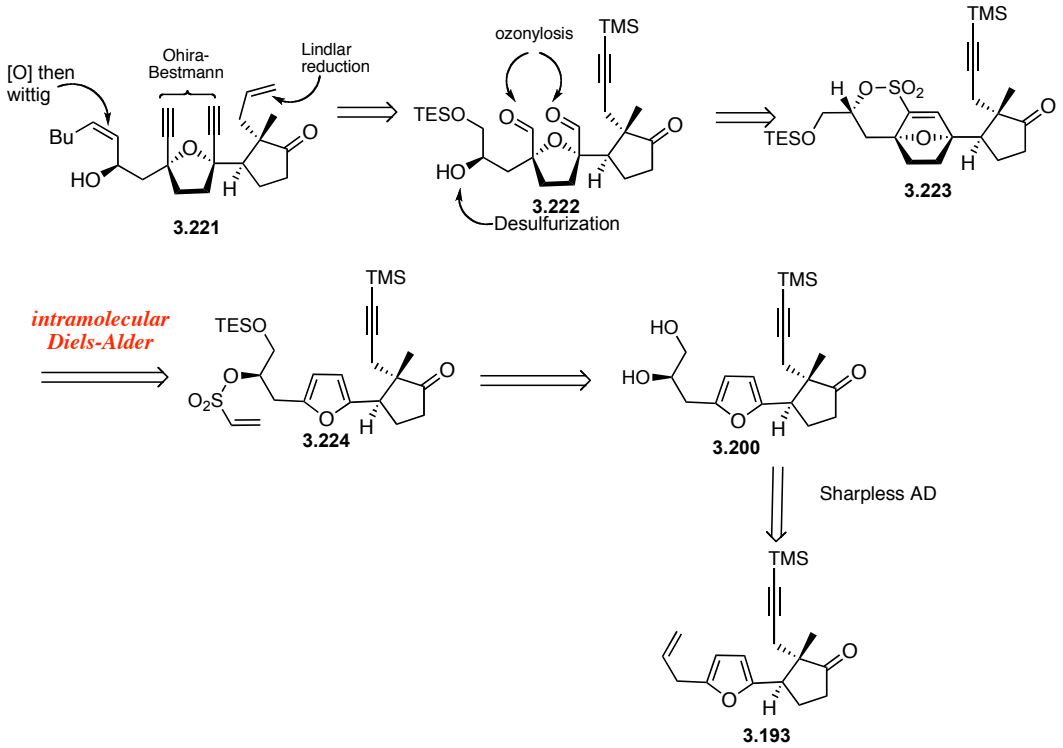
In response to the lack of methodologies available to achieve this transformation in high endo/exo-, regio-, and diastereoselectivity, we began our own methodological development in this area. Progress towards a solution to this problem has been made in the Martin group by Noah Benjamin and will be reported in due course. In the context of cortistatin A, however, a different solution to this problem was recently discovered that precludes the need to perform an intermolecular Diels-Alder reaction.

3.6.7 Altered Synthetic Route

Since the alkynylation step had proven to be far more problematic than anticipated, it was necessary to alter our synthetic approach. Because we had already previously discovered that ADMix was an effective dihydroxylation

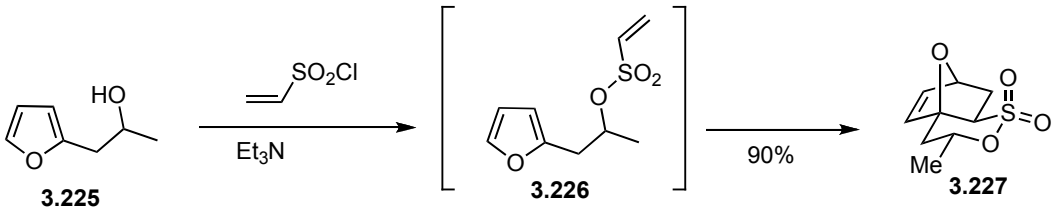
reagent for **3.193**, we postulated that the desired stereochemistry at C3 could be established via the Sharpless asymmetric dihydroxylation reaction. Subsequent transformation of the terminal alcohol into an alkene could be performed at a later stage to access **3.221**, but prior to the cascade RCM (Scheme 3.59). In addition, it occurred to us that an intramolecular Diels-Alder pathway would also be available if we functionalized the secondary alcohol as its vinyl sulfonate derivative **3.224**. Intramolecular Diels-Alder reactions are often much more facile, regio-, and stereoselective than their corresponding intermolecular variants and this was of interest to us.

Scheme 3.59



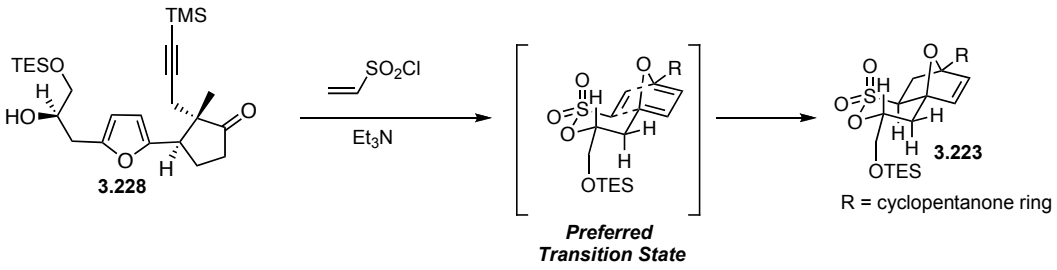
In this area, Metz and coworkers have reported an intramolecular Diels-Alder of **3.226** to give **3.227** (Scheme 3.60).[155] The reaction proceeded to give only a single diastereomer.[156] The vinylsulfonate intermediate **3.226** was not isolated as the ensuing Diels-Alder reaction occurs spontaneously.

Scheme 3.60

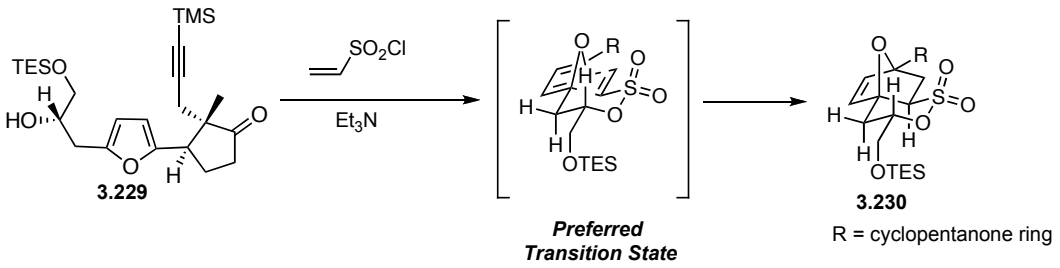


The stereochemistry of the secondary alcohol is important as it will direct the facial selectivity in the Diels-Alder reaction. In our strategy, the (*S*)-alcohol **3.229** would yield the wrong stereochemistry at the oxabicyclic bridgehead carbons (Scheme 3.62), but the (*R*)-alcohol **3.228** would furnish the desired adduct (Scheme 3.61). This is fortuitous since the (*R*)-alcohol has the stereochemistry required for later steps in the synthesis.

Scheme 3.61

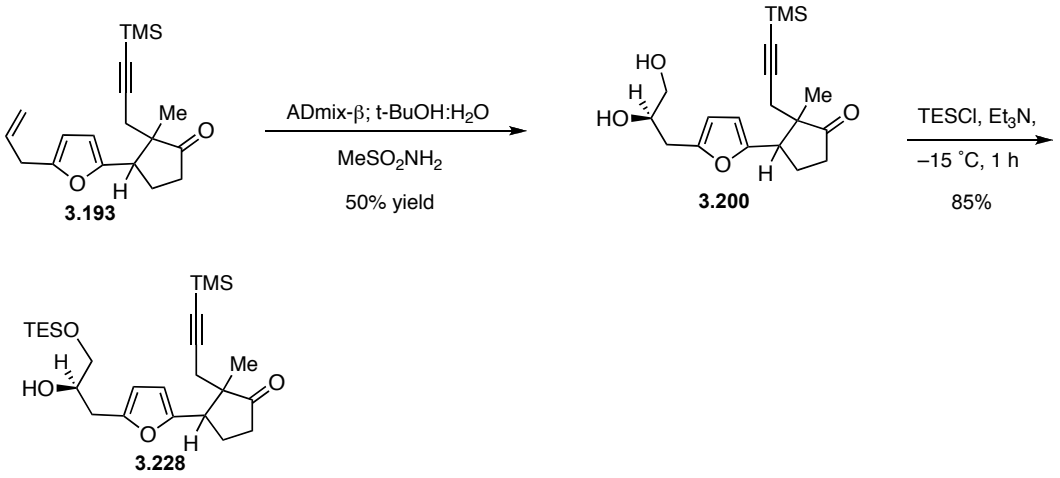


Scheme 3.62



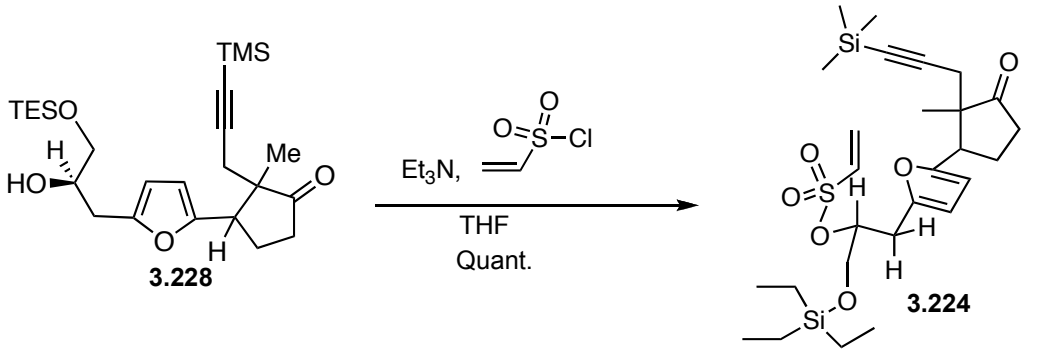
According to the Sharpless AD mnemonic, the desired (*R*)-alcohol will be produced using ADMix-β in the dihydroxylation step. In the event, racemic furan **3.193** was dihydroxylated to produce diol **3.200** in 50% yield. The primary alcohol was selectively protected as its TES ether **3.228** (Scheme 3.63).

Scheme 3.63



The alcohol was sulfonylated with vinylsulfonyl chloride to produce **3.224** in quantitative yield (Scheme 3.64). This intermediate was isolable and did not undergo spontaneous cycloaddition, although after standing at room temperature for several days in $CDCl_3$ cycloaddition products began to form.

Scheme 3.64



By heating furan **3.224** in benzene for 24 h, conversion to the Diels-Alder adduct **3.223** was complete, and a 95% yield of two diastereomers (1:1 ratio) was obtained (Scheme 3.65). Since we started from racemic furan **3.193**, the two diastereomers must differ in the stereochemistry of the chiral carbons that are α and β to the carbonyl group in the cyclopentanone ring. Furthermore, the fact that we only isolated two diastereomers is very promising because that is the minimum number of diastereomers that could be isolated after the Diels-Alder step is two, and this would only happen if both the dihydroxylation and Diels-Alder reactions had occurred with perfect diastereoselectivity. Gratifyingly, the two diasteromers were separable by silica chromatography and were fully characterized by NMR, IR, and mass spectrometry. A large coupling between H_a and H_b is present in the NMR spectrum for both diastereomers, which is consistent with an axial-axial coupling and thus the equatorial placement of the carbosiloxy moiety (Figure 3.14). Efforts are ongoing to obtain a crystal structure

of each individual diastereomer to verify their relative and absolute stereochemistry.

Scheme 3.65

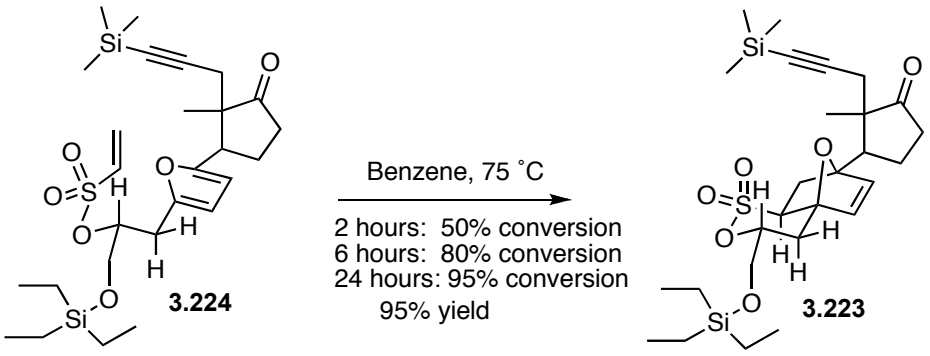
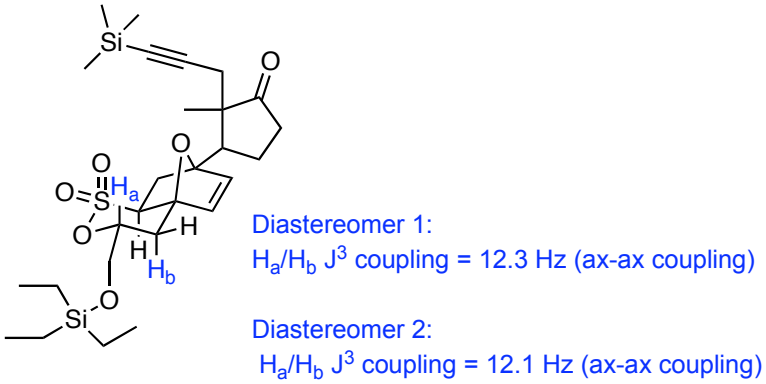


Figure 3.14



3.7 SUMMARY AND CONCLUSIONS

Cortistatin A is an exciting natural product that presents both valuable biological activity and novel structural challenges. The antiangiogenic properties of cortistatins A and J ensure that these natural products, as well as their analogs, will be continue to studied for years to come. Due to the lack of natural abundance of the marine sponge from which the cortistatins are derived, the need

for efficient methods to access these molecules is great. Progress has been made towards the establishment of practical syntheses of these compounds, but certainly room for improvement still exists.

At the outset of our studies, we identified three key synthetic transformations for which there existed little or no precedent. We successfully developed a solution for the first of those steps, an enantioselective conjugate addition of furan to cyclopentenone. We then extended our solution to developing a broad methodology that is applicable to many compounds beyond cortistatin A (see chapter 2). The second key step, an intermolecular, diastereoselective Diels-Alder reaction, was examined and we advanced the field in this area by extending this chemistry to 2,5-disubstituted furans. However, we eventually replaced this intermolecular reaction with an extraordinarily efficient intramolecular Diels-Alder reaction. This discovery broadens the existing methodology available for intramolecular Diels-Alder reactions with substituted furans. The third key step, a cascade RCM, was not examined but the Martin group plans to pursue this approach in the future.

We have accessed an advanced intermediate in our synthesis of cortistastin A by an approach that requires only 10 linear steps and proceeds in 17% overall yield (40% based on recovered starting material). Most of the steps used commercially available or inexpensive starting materials and were high yielding, including challenging transformations such as the installation of a quaternary carbon via an enolate alkylation and the intramolecular Diels-Alder cycloaddition.

Our synthetic route has the advantage that it can also access cortistatin J without any alteration, as well as a simpler core structure that could potentially be used for analog synthesis. These additional synthetic targets may also be pursued by the Martin group in the future.

Chapter 4: Experimental Procedures

4.1 General

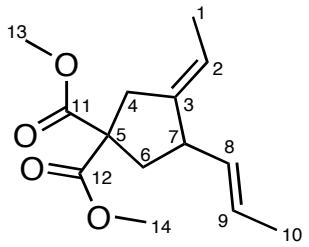
Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (CH_3OH), acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Toluene was dried by sequential passage through a column of activated neutral alumina followed by a column of Q5 reactant. Methylene chloride, triethylamine, and *NN*-diisopropylamine were distilled from calcium hydride prior to use. Benzene was distilled from sodium/benzophenone. Acetone was distilled from molecular sieves. All solvents were determined to contain less than 50 ppm H2O by Karl Fischer coulometric moisture analysis. All reactions were performed in flame-dried glassware under argon or nitrogen unless otherwise indicated. Volatile solvents were removed under reduced pressure using a Buchi rotary evaporator. Infrared (IR) spectra were obtained using a FTIR 1600 spectrophotometer using sodium chloride plates and reported as wave numbers. Low resolution chemical ionization mass spectra were obtained with a TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using 250 micron 60F-254 silica gel plates. The plates were visualized with UV light, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's

procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923) using ICN Silitech 32-63 D 60A silica gel.

^{1}H nuclear magnetic resonance (NMR) spectra were obtained at either 600, 500, or 400 MHz as solutions in $CDCl_3$ unless indicated otherwise. ^{13}C NMR were obtained at either 125, 100 or 75 MHz in the indicated deuterated solvent. Chemical shifts are reported in parts per million (ppm, δ), and referenced to TMS, and coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex; br, broad; and app, apparent.

Reagent Preparation. All reagents were freshly distilled or otherwise purified immediately prior to use. Cyclopentenone, cyclohexenone, and chlorotrimethylsilane were distilled over calcium hydride; furan, benzofuran, pyrrole, thiophene, benzothiophene were distilled over potassium hydroxide; 1-methyl-5,6-dihydropyridin-2(1*H*)-one, butenolide, and *N*-methylindole were prepared and purified according to known literature procedures;[157] titanium tetraisopropoxide was purchased from Aldrich (98% pure) and distilled; $ZnCl_2$ was fused under reduced pressure; [Rh(COD)acac] and $[RhCl(C_2H_4)]_2$ were purchased from STREM and used without purification; (*R*)-MeO-BIPHEP was received from Solvias and dried under vacuum prior to use. (*R*)-Tol-BINAP was purchased from STREM, and traces of phosphine oxide were removed via flash chromatography. Tetrahydrofuran (THF) was passed through a column of neutral alumina, stored under argon, and sparged with argon for 1 h immediately prior to use.

4.2 [Rh(CO)$_2$Cl]$_2$-Catalyzed Tandem catalysis methodology

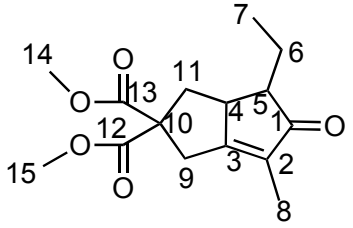


1.97

3-Ethylidene-4-((*E*)-prop-1-enyl)cyclopentane-1,1-dicarboxylate (1.114). To a to a solution of [Rh(CO)$_2$Cl]$_2$ (10 mol %) in degassed MeCN (0.75 mL) was added **1.117** (169 mg, 0.67 mmol) and the solution was stirred for 10 min at –40 ˚C. In a separate flask, **1.21** (50 mg, 0.27 mmol) was added to a slurry of NaH (16 mg, 0.41 mmol, 60% dispersion in mineral oil) in MeCN (2.0 mL) at room temperature, and the mixture was stirred for 30 min. The resulting solution of sodium enolate was then added *via* syringe to the solution of **1.117** and [Rh(CO)$_2$Cl]$_2$ at –40 ˚C. The reaction mixture was stirred for 6 h at –40 ˚C, whereupon it was transferred to a screw cap vial that was sealed and heated at 110 ˚C (bath temperature) until the intermediate enyne **1.113** was consumed (30 min). The reaction mixture was diluted with H_2O (2 mL) and Et_2O (2 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (5 x 2 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to furnish 49 mg (72%) of **1.114** as a pale yellow

oil: ^{1}H NMR (500 MHz) δ 5.50–5.41 (app ddq, *J* = 15.7, 6.4, 0.6 Hz, 1 H), 5.52-5.22 (comp, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.04–2.98 (comp, 2 H), 2.85-2.80 (m, 1 H), 2.52-2.48 (ddd, *J* = 12.9, 7.4, 1.8 Hz, 1 H), 1.92-1.87 (dd, *J* = 12.9, 11.6 Hz, 1 H), 1.69-1.67 (dd, *J* = 6.4, 1.6 Hz, 3 H), 1.61-1.55 (comp, 3 H); ^{13}C NMR (500 MHz) δ 172.5, 172.4, 141.4, 132.3, 126.8, 117.5, 58.5, 52.8, 52.7, 46.8, 40.9, 36.8, 17.9, 14.6; mass spectrum (CI) *m/z* 252.1361 [$C_{14}H_{20}O_4$ requires 252.1362] 253 (base), 252, 221, 193, 192.

NMR Assignments. ^{1}H NMR (500 MHz) δ 5.50–5.41 (app ddq, *J*= 15.7, 6.4, 0.6 Hz, 1 H, C9-H), δ 5.52-5.22 (comp, 2 H, C2-H & C8-H), δ 3.74 (s, 3 H, C13-H), δ 3.73 (s, 3 H, C14-H), δ 3.04–2.98 (comp, 2 H, C4-H & C7-H), δ 2.85-2.80 (m, 1 H, C4-H), δ 2.52–2.48 (ddd, *J*=12.9, 7.4, 1.8 Hz, 1 H, C6-H), δ 1.92-1.87 (dd, *J*=12.9, 11.6 Hz, 1 H, C6-H), δ 1.69-1.67 (dd, *J*=6.4, 1.6 Hz, 3 H, C10-H), δ 1.61-1.55 (comp, 3 H, C1-H); ^{13}C NMR (500 MHz) δ 172.5 (C11), 172.4 (C12), 141.4 (C3), 132.3 (C8), 126.8 (C9), 117.5 (C2), 58.5 (C5), 52.8 (C13), 52.7 (C14), 46.8 (C7), 40.9 (C6), 36.8 (C4), 17.9 (C10), 14.6 (C1).

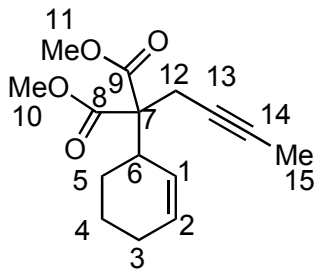


1.118

Dimethyl 4-ethyl-6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (1.118). To a solution of $[Rh(CO)_2Cl]_2$ (10 mol %) in degassed PhMe (1.25 mL) was added **1.113** (30 mg, 0.126 mmol), and the

solution was stirred for 20 min at room temperature. The mixture was then sealed in a screw cap vial under an atmosphere of argon and heated to 110 ˚C for 15 min. The reaction mixture was cooled to room temperature and was then filtered through a short plug of silica gel eluting with Et_2O (15 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to yield **1.118** as a minor side-product: ^{1}H NMR (500 MHz) δ 3.79 (s, 3 H), 3.76 (s, 3 H), 3.27 (d, J = 17.1 Hz, 1 H), 3.12 (d, J = 17.1 Hz, 1 H), 3.11–3.06 (m, 1 H), 2.64 (dd, J = 12.6, 7.3 Hz, 1 H), 2.43 (dt, J = 11.7, 6.2 Hz, 1 H), 1.82 (t, J = 12.99 Hz, 1 H), 1.71–1.69 (m, 3 H), 1.63 (dqd, J = 15.1, 7.5, 5.4 Hz, 1 H), 1.32–1.26 (m, 1 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (500 MHz) δ 211.8, 176.2, 172.1, 171.6, 131.3, 60.4, 53.2, 53.1, 50.6, 46.5, 34.7, 34.0, 22.2, 13.1, 8.5; mass spectrum (CI) m/z 281.1383 [$C_{15}H_{21}O_5$ requires 281.1388] 309, 281 (base).

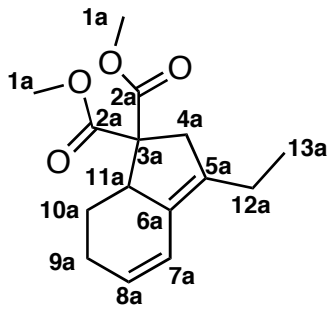
NMR Assignments: ^{1}H NMR (500 MHz) δ 3.79 (s, 3 H, C15-H), 3.76 (s, 3 H, C14-H), 3.27 (d, J = 17.1 Hz, 1 H, C9-H), 3.12 (d, J = 17.1 Hz, 1 H, C9-H), 3.11–3.06 (m, 1 H, C4-H), 2.64 (dd, J = 12.8, 7.3 Hz, 1 H, C11-H), 2.43 (dt, J = 11.7, 6.2 Hz, 1 H, C5-H), 1.82 (app t, J = 12.8 Hz, 1 H, C11-H), 1.71–1.69 (m, 3 H, C8-H), 1.63 (dqd, J = 15.1, 7.5, 5.4 Hz, 1 H, C6-H), 1.32–1.26 (m, 1 H, C6-H), 1.04 (t, J = 7.4 Hz, 3 H, C7-H); ^{1}H NMR (500 MHz) δ 211.8 (C1), 176.2 (C3), 172.1 (12), 171.6 (C13), 131.3 (C2), 60.4 (C10), 53.2 (C14), 53.1 (C15), 50.6 (C5), 46.5 (C4), 34.7 (C11), 34.0 (C9), 22.2 (C6), 13.1 (C7), 8.5 (C8).



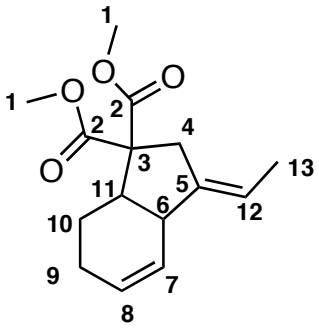
1.125

Dimethyl 2-(but-2-ynyl)-2-(cyclohex-2-enyl)malonate (1.125) (AJS-II-16). Allylic trifluoroacetate **1.124** (100 mg, 0.52 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (10 mol%, 8 mg, 0.021 mmol) in CH_3CN (1 mL), and the solution was stirred for 10 min at room temperature. In a separate flask malonate **1.21** (0.21 mmol) was added to a slurry of NaH (60% w/w in mineral oil, 0.42 mmol) in CH_3CN (1 mL) at room temperature, and the mixture was stirred for 30 min. The resulting sodium enolate was added *via* syringe to the solution of **1.124** and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then sealed in a screw cap vial under an atmosphere of argon, and heated to 110 ˚C for 45 min. The reaction mixture was cooled to room temperature and was then filtered through a short plug of silica gel eluting with Et_2O (25 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et2O (5:1) to furnish 40 mg (72%) of **1.125** as a colorless oil. ^{1}H NMR (500 MHz) δ 5.78–5.70 (comp, 2 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.14–3.08 (m, 1 H), 2.84 (dq, J = 17.1, 2.5 Hz, 1 H), 2.76 (dq, J = 17.1, 2.5 Hz, 1 H), 1.96–1.93 (comp, 2 H), 1.88–1.76 (comp, 2 H), 1.75 (t, J = 2.5 Hz, 3 H), 1.61–1.52 (m, 1 H), 1.37–1.29 (m, 1 H); ^{13}C NMR (100 MHz) δ 170.7, 170.4, 128.7, 127.7, 78.7, 73.8, 60.7, 52.4, 52.2, 38.7, 24.9, 24.2, 23.0, 22.3, 3.6.

NMR Assignments: ^{1}H NMR (500 MHz) δ 5.78–5.70 (comp, 2 H, C1-H & C2-H), 3.75 (s, 3 H, C8-H), 3.70 (s, 3 H, C9-H), 3.14–3.08 (m, 1 H, C6-H), 2.84 (dq, J = 17.1, 2.5 Hz, 1 H, C12-H), 2.76 (dq, J = 17.1, 2.5 Hz, 1 H, C12-H), 1.96–1.93 (comp, 2 H, C3-H), 1.88–1.76 (comp, 2 H, C4-H & C5H), 1.75 (t, J = 2.5 Hz, 3 H, C15-H), 1.61–1.52 (m, 1 H, C4-H), 1.37–1.29 (m, 1 H, C5-H); ^{13}C NMR (100 MHz) δ 170.7 (C8), 170.4 (C9), 128.7 (C1), 127.7 (C2), 78.7 (C13), 73.8 (C14), 60.7 (C7), 52.4 (C10), 52.2 (C11), 38.7 (C6), 24.9 (C3), 24.2 (C5), 23.0 (C12), 22.3 (C4), 3.6 (C15).



1.127



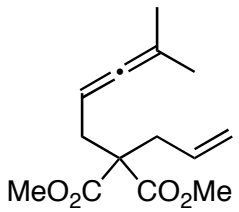
1.126

Procedure for the $[Rh(CO)_2Cl]_2$-Catalyzed Tandem Allylic Alkylation/ Cycloisomerization to furnish (*E*)-dimethyl 3-ethylidene-3,3a,7,7a-tetrahydro-1*H*-indene-1,1(2*H*,6*H*)-dicarboxylate (1.126) and dimethyl 3-ethyl-7,7a-dihydro-1*H*-indene-1,1(2*H*,6*H*)-dicarboxylate (1.127). Allylic trifluoroacetate **1.117** (130mg, 0.67 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (10 mol%, 17 mg, 0.045 mmol) in MeCN (0.75 mL), and the solution was stirred for 10 min at 0 ˚C. In a separate flask, malonate **1.21** (83mg,

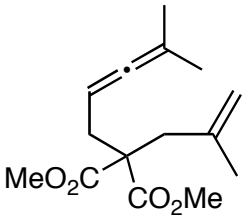
0.45 mmol) was added to a slurry of NaH (60% dispersion in mineral oil, 22mg, 0.54 mmol) in MeCN (2.0 mL) at room temperature, and the mixture was stirred for 30 min. The resulting solution of sodium enolate was then added *via* syringe to the solution of **1.117** and $[Rh(CO)_2Cl]_2$ at ambient temperature. The reaction mixture was stirred for 1 h at rt, then sealed in a screw cap vial and heated to 110 ˚C in the microwave (300 W, cooling) for 30 minutes. The reaction mixture was filtered through a plug of silica gel with Et_2O and then concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to furnish an inseparable mixture of **1.126** and **1.127** (40–65%, ca. 3:1 ratio of **1.126:1.127**): ^{1}H NMR (500 MHz) δ 6.24 (dd, J = 9.8, 2.5 Hz, 0.25 H), 5.85–5.81 (m, 0.75 H), 5.73–5.68 (m, 1 H), 5.22–5.16 (m, 0.75 H), 3.73 (s, 0.75 H), 3.72 (s, 2.25 H), 3.70 (s, 2.25 H), 3.67 (s, 0.75), 3.48 (br d, J = 13.3 Hz, 0.25 H), 3.21–3.16 (comp, 1.5 H), 3.05 (d, J = 17.0 Hz, 0.25 H), 2.81–2.76 (comp, 1.5 H), 2.65 (d, J = 17.0 Hz, 0.25 H), 2.26–2.12 (m, 1 H), 2.06–1.95 (m, 1.75 H), 1.59–1.56 (m, 2.25 H), 1.29–1.23 (m, 0.75H), 1.16–1.05 (m, 1 H), 1.00 (t, J = 15.2 Hz, 0.75 H); ^{13}C NMR (125 MHz) δ 172.6, 172.4, 171.2, 170.5, 142.0, 134.4, 129.8, 128.7, 126.9, 126.1, 121.5, 117.3, 62.4, 61.6, 52.7, 52.5, 51.9, 49.5, 42.9, 42.8, 42.7, 34.5, 26.3, 25.6, 24.7, 21.1, 20.6, 14.7, 12.5; MS (CI/CH_4) m/z (rel intensity, %) 293($[M+C_2H_5]^+$,16), 265 ($[M+H]^+$,82), 205 ($[M–CO_2Me]^+$,100), 145 ($[M–C_2O_4Me_2H]^+$,24).

NMR Assignments. ^{1}H NMR (500 MHz) δ 6.24 (dd, J = 9.8, 2.5 Hz, 0.25 H, C7a-H), 5.85–5.81 (m, 0.75 H, C7-H), 5.73–5.68 (m, 1 H, C8-H & C8a-H), 5.22–5.16 (m, 0.75 H, C12-H), 3.73 (s, 0.75 H, C1a-H), 3.72 (s, 2.25 H, C1-H),

3.70 (s, 2.25 H, C1-H), 3.67 (s, 0.75, C1a-H), 3.48 (br d, J = 13.3 Hz, 0.25 H, C11a-H), 3.21–3.16 (comp, 1.5 H, C6-H & C4-H), 3.05 (d, J = 17.0 Hz, 0.25 H, C4a-H), 2.81–2.76 (comp, 1.5 H, C11-H & C4-H), 2.65 (d, J = 17.0 Hz, 0.25 H, C4a-H), 2.26–2.12 (m, 1 H, C9a-H, C12a-H), 2.06–1.95 (m, 1.75 H, C9-H & C10a-H), 1.59–1.56 (m, 2.25 H, C13-H), 1.29–1.23 (m, 0.75H, C10-H), 1.16–1.05 (m, 1 H, C10a-H & C10-H), 1.00 (t, J = 15.2 Hz, 0.75 H, C13a-H); ^{13}C NMR (125 MHz) δ 172.6 (C2a), 172.4 (C2), 171.2 (C2a), 170.5 (C2), 142.0 (C5), 134.4 (C5a), 129.8 (C6a), 128.7 (C8a), 126.9 (C7), 126.1 (C8), 121.5 (C7a), 117.3 (C12), 62.4 (C3), 61.6 (C3a), 52.7 (C1), 52.5 (C1 & C1a overlap), 51.9 (C1a) , 49.5 (C11a), 42.9 (C11), 42.8 (C6), 42.7 (C4a), 34.5 (C4), 26.3 (C9a), 25.6 (C10a), 24.7 (C9), 21.1 (C10), 20.6 (C12a), 14.7 (C13), 12.5 (C13a).



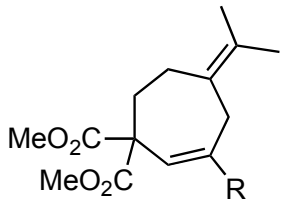
1.54



1.55

General Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allenic Alkylation to furnish dimethyl-2-allyl-2-(4-methylpenta-2,3-dienyl)malonate (1.54) or dimethyl-2-(2-methylallyl)-2-(4-methylpenta-2,3-dienyl)malonate (1.55). Allenic carbonate **1.143** (1.0 mmol) was added to a solution of [Rh(CO)$_2$Cl]$_2$ (10 mol%, 0.1 mmol, 39 mg) in CH_3CN (5 mL), and the solution was stirred for 10 min at room temperature. In a separate flask malonate **1.144** or **1.145** (1.5 mmol) was added to a slurry of NaH (60% w/w in mineral oil, 1.4 mmol) in CH_3CN (5

mL) at room temperature, and the mixture was stirred for 20 min. The resulting sodium enolate was added *via* syringe to the solution of **1.143** and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then sealed in a screw cap vial under an atmosphere of argon, and stirring was continued until the starting carbonate was consumed (as indicated by TLC analysis). The reaction was then filtered through a short plug of silica gel eluting with Et_2O (50 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to furnish **1.54** or **1.55**. Spectroscopic data matched that previously reported in the literature.[8]

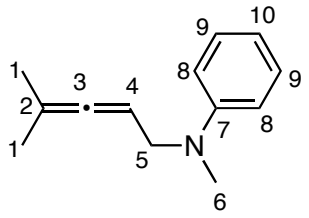


R = H: **1.56**

R = Me: **1.57**

Procedure for the $[Rh(CO)_2Cl]_2$-Catalyzed Tandem Allylic Alkylation/Cycloisomerization to furnish dimethyl-5-(propan-2-ylidene)cyclohept-2-ene-1,1-dicarboxylate (1.56) or dimethyl-3-methyl-5-(propan-2-ylidene)cyclohept-2-ene-1,1-dicarboxylate (1.57). Allenic trichloroacetate **1.148** (0.45 mmol, 110 mg) was added to a solution of $[Rh(CO)_2Cl]_2$ (10 mol%, 0.045 mmol, 17 mg), triphenylphosphine (20 mol%, 0.09 mmol, 24 mg), and silver hexafluoroantiminate (30 mol%, 0.14, 48 mg), in MeCN (1.5 mL), and the solution was stirred for 10 min at 0 ˚C. In a separate

flask, malonate **1.144** or **1.145** (0.67 mmol) was added to a slurry of NaH (60% dispersion in mineral oil, 0.63 mmol) in MeCN (2.0 mL) at room temperature, and the mixture was stirred for 30 min. The resulting solution of sodium enolate was then added via syringe to the solution of **1.148** and $[Rh(CO)_2Cl]_2$ at ambient temperature. The resultant solution was stirred until the starting trichloroacetate was consumed (as indicated by TLC analysis). The argon atmosphere was then exchanged for a CO atmosphere, and the vial was sealed with a screw cap and heated to 110 °C in the microwave (300 W, cooling) for 15 min. The reaction mixture was filtered through a plug of silica gel with Et_2O and then concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to furnish **1.56** in 72% yield and **1.57** in 75% yield. Spectroscopic data matched with that previously reported in the literature.[8]

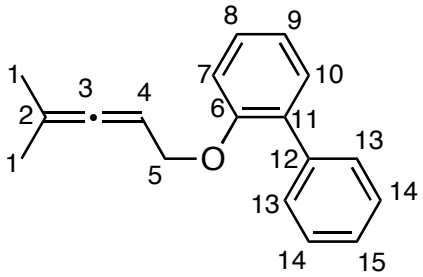


1.164

***N*-Methyl-*N*-(4-methylpenta-2,3-dienyl)aniline (1.164).** Allenic carbonate **1.143** (25 mg, 0.16 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (10 mol%, 0.016 mmol, 6 mg) and tetrabutylammonium iodide (20 mol%, 0.032 mmol, 12 mg) in MeCN (1.6 mL), and the solution was stirred for 5 min at room temperature. *N*-methylaniline (43 mg, 0.40 mmol) was added to the reaction mixture *via* syringe. The mixture was stirred at room temperature for 16 h, under

an atmosphere of argon, and then heated to 60 ˚C (oil bath temperature) for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with pentane/Et_2O (10:1) to yield **1.164** (29 mg, 99%) as an amber-colored oil: ^{1}H NMR (500 MHz) δ 7.25–7.19 (m, 2H), 6.75–6.72 (m, 2H), 6.69–6.66 (dddd, J = 7.3, 7.3, 0.98, 0.98 Hz, 1H), 4.95–4.91 (m, 1H), 3.90 (d, J = 5.9 Hz, 2 H), 2.93 (s, 3H), 1.59 (s, 3 H), 1.59 (s, 3H); ^{13}C NMR (125 MHz) δ 204.5, 151.2, 130.9, 118.3, 114.8, 98.5, 86.3, 54.0, 39.9, 22.3; IR (thin film) 2906, 2359, 1961, 1599, 1505, 1362, 1200, 748, 690 cm^{-1}; HRMS calculated for $C_{13}H_{17}N$ 188.1439, found 188.1435.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.25–7.19 (m, 2H, C9-H), 6.75–6.72 (m, 2H, C8-H), 6.69–6.66 (dddd, J = 7.3, 7.3, 0.98, 0.98 Hz, 1H, C10-H), 4.95–4.91 (m, 1H, C4-H), 3.90 (d, J = 5.9 Hz, 2 H, C5-H), 2.93 (s, 3H, C6-H), 1.59 (s, 3H, C1-H), 1.59 (s, 3H, C1-H); ^{13}C NMR (125 MHz) δ 204.5 (C3), 151.2 (C7), 130.9 (C9), 118.3 (C10), 114.8 (C8), 98.5 (C2), 86.3 (C4), 54.0 (C5), 39.9 (C6), 22.3 (C1).



1.166

2-(4-Methylpenta-2,3-dienyloxy)biphenyl (1.166) (AJS-III-48). Allenic carbonate **1.143** (25 mg, 0.16 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (10 mol%, 0.016, 6 mg) in THF (0.8 mL), and the solution was stirred for 5 min at room temperature. In a separate flask, a solution of LiHMDS (1 M in THF, 0.32 mL) was added *via* syringe to a solution of *o*-phenylphenol (68 mg, 0.40 mmol), copper(I) iodide (76 mg, 0.40 mmol), and dry THF (0.8 mL) at room temperature, followed by stirring for approximately 20 min and transfer *via* syringe to the solution of $[Rh(CO)_2Cl]_2$ and **1.143**. The resultant mixture was stirred at room temperature for 16 h, under an atmosphere of argon and then heated to 60 ˚C (oil bath temperature) for 1 h. The reaction was diluted with water (2 mL) and Et_2O (2 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 1 mL) and the combined organic fractions were dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography, eluting with pentane/Et_2O (10:1) to yield **1.166** as a colorless oil: ^{1}H NMR (400 MHz) δ 7.57–7.54 (m, 2H), 7.41–7.25 (m, 5H), 7.03–6.99 (m, 2H), 5.15–5.09 (m, 1H), 4.53 (d, J = 6.1 Hz, 2H), 1.65 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz) δ 202.9, 155.2, 138.7, 131.1, 130.9, 129.6, 128.3, 127.9, 126.8, 120.9, 113.4, 97.2, 85.7, 66.8, 20.1; IR (thin film) 2980(m), 2908(m), 1969(w), 1481(s), 1434(s), 1212(s), 1005(s), 751(s), 698(s) cm^{-1}; HRMS calculated for $C_{18}H_{18}O$ 241.1436, found 251.1442.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.57–7.54 (m, 2H, aromatic C-H), 7.41–7.25 (m, 5H, aromatic C-H), 7.03–6.99 (m, 2H, aromatic C-H), 5.15–5.09 (m, 1H, C4-H), 4.53 (d, J = 6.1 Hz, 2H, C5-H), 1.65 (s, 3H, C1-H), 1.65 (s,

3H, C1-H); ^{13}C NMR (125 MHz) δ 202.9 (C3), 155.2 (C6), 138.7 (C12), 131.1 (C11), 130.9 (C8), 129.6 (C14), 128.3 (C15), 127.9 (C13), 126.8 (C10), 120.9 (C9), 113.4 (C7), 97.2 (C2), 85.7 (C4), 66.8 (C5), 20.1 (C1); IR (thin film) 2980(m), 2908(m), 1969(w), 1481(s), 1434(s), 1212(s), 1005(s), 751(s), 698(s) cm^{-1}; HRMS cacld for $C_{18}H_{18}O$ 241.1436, found 251.1442.

4.3 ENANTIOSELECTIVE CONJUGATE ADDITION METHODOLOGY

General Procedure for the Preparation of Heteroaryl Titanates. Solutions of the 2-lithiated heterocycles were prepared by deprotonation in THF according to known literature procedures.[157] A 0.5 M solution of the lithiated heterocycle in THF was transferred via cannula to a 1 M solution of titanium tetraisopropoxide, which had been distilled immediately prior to use, in THF at –78 ˚C. The resultant mixture was stirred for 45 min at –78 ˚C and used immediately.

General Procedure for the Preparation of 2-Heteroaryl Zinc Chlorides. Solutions of the 2-lithiated heterocycles were prepared in THF according to known literature procedures.[157] A 0.5 M solution of the lithiated heterocycle in THF was transferred via cannula to a 1 M solution of freshly fused $ZnCl_2$ in THF at 0 ˚C. The resultant mixture was stirred for 45 min at 0 ˚C and used immediately.

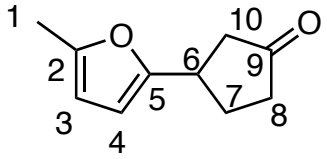
Determination of Enantiomeric Excess. Enantiomers were separated via chiral HPLC with an AD or OD-H DAICEL chiral column, using a 90:10 to 99:1 solvent ratio of hexanes to isopropanol as the solvent system, at flow rates of 0.5–1.0 mL/min. HPLC analysis was performed on the derivative alcohols, formed by

$NaBH_4$ reduction of the conjugate addition product, for compounds **2.100**, **2.118**, **2.148**, and **2.138**.

General Procedure for Procedure for Deuterium Quench of 2-Heteroaryllithium Compounds. Solutions of the 2-lithiated heterocycles were prepared in THF according to known literature procedures.[157] The reaction mixture was then quenched with CD_3OD at 0 ºC. The organic layer was extracted with Et_2O, dried ($MgSO_4$), and concentrated under reduced pressure. ^1H NMR analysis was performed on the crude product.

General Procedure for Enantioselective Conjugate Addition Employing 2-Heteroaryl Titanates (Method A). A solution of [Rh(acac)((*R*)-MeO-BIPHEP)] was generated by heating [Rh(acac)(COD)] (9.3 mg, 0.03 mmol) and (*R*)-MeO-BIPHEP (19 mg, 0.033 mmol) in THF (1 mL) for 30 min at 50 °C. The Michael acceptor (0.3 mmol) and $ClSiMe_3$ (49 mg, 0.45 mmol, 58 mL) were added, and the solution was cooled to –78 °C, whereupon the solution of the 2-heteroaryl titanate (0.6 mmol) was added via cannula. The resultant mixture was stirred at –78 ˚C for 30 min (unless otherwise indicated) and then at room temperature until the starting material was consumed (as indicated by TLC analysis).[158] Aqueous 1 N HCl (1 mL) was added, and the resultant solution was stirred for 20 min. The layers were separated, and the aqueous layer was extracted with Et_2O (5 x 3 mL) or EtOAc (5 x 3 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography to yield the addition product.

General Procedure for Enantioselective Conjugate Addition Employing 2-Heteroaryl Zinc Chlorides (Method B). A solution of [Rh(acac)((*R*)-MeO-BIPHEP)] was generated by heating [Rh(acac)(COD)] (9.3 mg, 0.03 mmol) and (*R*)-MeO-BIPHEP (19 mg, 0.033 mmol) in THF (1 mL) for 30 min at 50 °C. The Michael acceptor (0.3 mmol) and $ClSiMe_3$ (49 mg, 0.45 mmol, 58 mL) were added, and the solution was cooled to –78 °C, whereupon the solution of the 2-heteroaryl zinc chloride (0.6 mmol) was added via cannula. The resultant mixture was then stirred at room temperature until the starting material was consumed (as indicated by TLC analysis).[159] Aqueous 1 N HCl (1 mL) was added, and the resultant solution was stirred for 20 min. The layers were separated, and the aqueous layer was extracted with Et_2O (5 x 3 mL) or EtOAc (5 x 3 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography to yield the addition product.

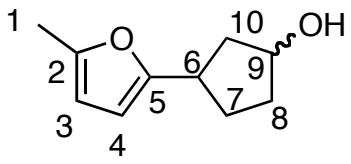


2.100

3-(5-Methylfuran-2-yl)cyclopentanone (2.100). Adduct **2.100** was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to yield 44 mg (90%) of **2.100**

as a colorless oil; ^{1}H NMR (600 MHz) δ 5.92 (d, J = 3.0 Hz, 1 H), 5.86 (d, J = 3.0 Hz, 1 H), 3.47-3.42 (m, 1 H), 2.56 (dd, J = 18.4, 8.2 Hz, 1 H), 2.42-2.32 (comp, 3 H), 2.26-2.21 (m, 1 H), 2.22 (s, 3 H), 2.12-2.06 (m, 1 H); ^{13}C NMR (150 MHz) δ 218.4, 154.8, 151.2, 105.9, 105.2, 43.7, 37.8, 35.5, 28.6, 13.5; IR ($CDCl_3$) 2967, 2921, 1744, 1612, 1570, 1405, 1218, 1150, 1022, 784 cm^{-1}; mass spectrum (CI) m/z 165.0916 [$C_{10}H_{13}O_2$ (M+1) requires 165.0916], 133, 165 (base), 193. 90% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; first enantiomeric pair; 16.5, 16.8 (Maj); second enantiomeric pair; 17.6, 21.2 (Maj).

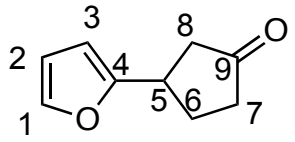
NMR Assignments: δ 5.92 (d, J = 3.0 Hz, 1 H, C3-H), 5.86 (d, J = 3.0 Hz, 1 H, C4-H), 3.47-3.42 (m, 1 H, C6-H), 2.56 (dd, J = 18.4, 8.2 Hz, 1 H, C10-H), 2.42-2.32 (comp, 3 H, C7-H, C8-H, & C10-H), 2.26-2.21 (m, 1 H, C8-H), 2.22 (s, 3 H, C1-H), 2.12-2.06 (m, 1 H, C7-H); ^{13}C NMR (150 MHz) δ 218.4 (C9), 154.8 (C5), 151.2 (C2), 105.9 (C3), 105.2 (C4), 43.7 (C10), 37.8 (C8), 35.5 (C6), 28.6 (C7), 13.5 (C1).



3-(5-Methylfuran-2-yl)cyclopentanol. (AJS-III-235). (Prepared for determination of the enantiomeric excess of **2.100**.) $NaBH_4$ (14 mg, 0.38 mmol) was added in one portion to a solution of furan **2.100** (52 mg, 0.32 mmol) in THF/MeOH (1mL/1mL) at 0 ˚C. The reaction was warmed to room temperature and stirred for an additional 1.5 h, whereupon H_2O (2 mL) was added. The

aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Pentane/Et_2O (4:1) to yield 42 mg (90%) of 3-(5-methylfuran-2-yl)cyclopentanol as a 3:1 cis/trans mixture as a colorless oil: ^{1}H NMR (500 MHz) δ 5.89 (dd, J = 2.9, 0.4 Hz, 0.75 H), 5.85-5.83 (m, 1.25 H), 4.47 (dddd, J = 2.5, 2.5, 5.2, 5.2 Hz, 0.25 H), 4.38 (m, 0.75 H), 3.38 (app p, J = 8.0, 0.25 H), 3.10 (app p, J = 8.0 Hz, 0.75 H), 2.35 (ddd, J = 6.3, 8.8, 13.7 Hz, 1 H), 2.25 (s, 3 H), 2.21-1.62 (comp, 5.25 H) ; ^{13}C NMR (125 MHz) δ 157.3 , 150.4, 105.7, 105.6, 104.2, 104.1, 73.6, 73.5, 41.6, 41.2, 36.8, 36.2, 35.6, 35.1, 29.7, 29.6, 13.6; IR ($CDCl_3$) 3346, 2958, 2922, 2873, 1616, 1569, 1438, 1342, 1220, 1082, 1021, 1000, 944, 779 cm^{-1}; mass spectrum (CI) m/z 167.1073 [$C_{10}H_{13}O_2$ (M+1) requires 167.1072], 149 (base), 167.

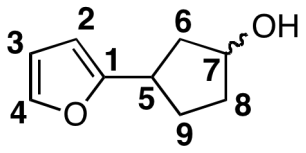
NMR Assignments: ^{1}H NMR (500 MHz) δ 5.89 (dd, J = 2.9, 0.4 Hz, 0.75 H, C3-H)), 5.85-5.83 (m, 1.25 H, C4-H), 4.47 (dddd, J = 2.5, 2.5, 5.2, 5.2 Hz, 0.25 H, C9-H), 4.38 (m, 0.75 H, C9-H), 3.38 (app p, J = 8.0, 0.25 H, C6-H), 3.10 (app p, J = 8.0 Hz, 0.75 H, C6-H), 2.35 (ddd, J = 6.3, 8.8, 13.7 Hz, 1 H, C10-H), 2.25 (s, 3 H, C1-H), 2.21-1.62 (comp, 5.25 H, C10-H, C8-H, C7-H, & O-H); ^{13}C NMR (125 MHz) δ 157.3 (C2), 150.4 (C5), 105.7 (C3), 105.6 (C3), 104.2 (C4), 104.1 (C4), 73.6 (C9), 73.5 (C9), 41.6 (C6), 41.2 (C6), 36.8 (C10), 36.2 (C10), 35.6 (C8), 35.1 (C8), 29.7 (C7), 29.6 (C7), 13.6 (C1).



2.118

3-(Furan-2-yl)cyclopentanone (2.118). Adduct **2.118** was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to yield 41 mg (90%) of **2.118** as a colorless oil; ^{1}H NMR (600 MHz) δ 7.34 (dd, J = 1.8, 0.7 Hz, 1 H), 6.30 (dd, J = 3.2, 1.8 Hz, 1 H), 6.06 (dt, J = 3.2, 0.7 Hz, 1 H), 3.53-3.48 (m, 1 H), 2.59 (dd, J = 18.2, 7.8 Hz, 1 H), 2.42-2.34 (comp, 3 H), 2.30–2.23 (m, 1 H), 2.14–2.08 (m, 1 H); ^{13}C NMR (150 MHz) δ 217.7, 156.6, 141.6, 110.1, 104.6, 43.5, 37.8, 35.5, 28.6; IR ($CDCl_3$) 2968, 2901, 1742, 1507, 1405, 1152, 1012, 736 cm^{-1}; mass spectrum (CI) m/z 151.0759 [$C_9H_{11}O_2$ (M+1) requires 151.0759], 151 (base). 97% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; first enantiomeric pair; 16.8 (Maj), 17.8; second enantiomeric pair; 20.8, 26.1 (Maj).

NMR Assignments. ^{1}H NMR (600 MHz) δ 7.34 (dd, J = 1.8, 0.7 Hz, 1 H, C1-H), 6.30 (dd, J = 3.2, 1.8 Hz, 1 H, C2-H), 6.06 (dt, J = 3.2, 0.7 Hz, 1 H, C3-H), 3.53-3.48 (m, 1 H, C5-H), 2.59 (dd, J = 18.2, 7.8 Hz, 1 H, C8-H), 2.42-2.34 (comp, 3 H, C8-H, C7-H, & C6-H), 2.30–2.23 (m, 1 H, C7-H), 2.14–2.08 (m, 1 H, C6-H); ^{13}C NMR (150 MHz) δ 217.7 (C9), 156.6 (C4), 141.6 (C1), 110.1 (C2), 104.6 (C3), 43.5 (C8), 37.8 (C7), 35.5 (C5), 28.6 (C6).

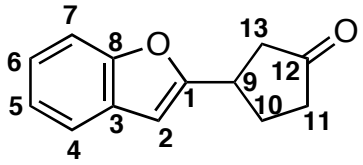


2.119

3-(Furan-2-yl)cyclopentanol (2.119). (AJS-V-160). (Prepared for determination of the enantiomeric excess of **2.118**). To a solution of **2.118** (40 mg, 0.26 mmol) in THF (0.75 mL) and MeOH (0.75 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at 0 °C. After 30 minutes an aqueous solution of NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added. The layers were separated, and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/EtOAc (2:1) to yield 40 mg (100%) of **2.119** as a colorless oil: ^{1}H NMR (500 MHz) in $CDCl_3$ δ 5.89 (dd, *J*= 4.0, 0.5 Hz, 1H), 5.83-5.85 (m, 1.6 H), 4.47 (sep, *J* = 3.5, 0.3 H), 4.38 (m, 1 H), 3.38 (p, *J*= 10.5 Hz, 0.3 H), 3.10 (p, *J*= 10.5 Hz, 1 H), 2.30-2.38 (m, 1 H), 2.25 (s, 4H), 1.62-2.21 (comp, 8.8 H); ^{13}C NMR (125 MHz) in $CDCl_3$ δ 157.3, 150.4, 105.7, 105.6, 104.2, 104.1, 73.6, 73.5, 41.6, 41.2, 36.9, 36.2, 35.6, 35.1, 29.7, 13.6; IR 3326, 2957, 1568, 1437, 1219, 1021, 779 cm^{-1}; mass spectrum (CI) *m/z* 167.107 ($C_9H_{11}SO$ (M+1) requires 167.107), 167 (base). 0% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; first enantiomeric pair; 16.5, 16.8 (Maj); second enantiomeric pair; 17.6, 21.2 (Maj).

NMR ASSIGNMENTS: ^{1}H NMR (500 MHz) in $CDCl_3$ δ 5.89 (dd, J= 4.0, 0.5 Hz, 1H, C2-H or C3-H), 5.83-5.85 (m, 1.6 H, C2-H & C3-H), 4.47 (sep, J

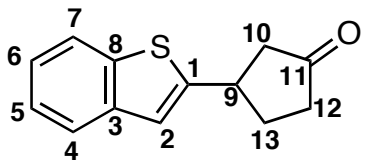
= 3.5, 0.3 H, C5-H), 4.38 (m, 1 H, C5-H), 3.38 (p, J= 10.5 Hz, 0.3 H, C7-H), 3.10 (p, J= 10.5 Hz, 1 H, C7-H), 2.30-2.38 (m, 1 H, OH), 2.25 (s, 4H, C10-H), 1.62-2.21 (comp m, 8.8 H, C8-H & C9-H & C6-H); ^{13}C NMR (125 MHz) in $CDCl_3$ δ 157.3 (C1), 150.4 (C4), 105.7 (C3), 105.6 (C3), 104.2 (C2), 104.1 (C2), 73.6 (C7), 73.5 (C7), 41.6 (C6), 41.2 (C6), 36.9 (C5), 36.2 (C5), 35.6 (C8), 35.1 (C8), 29.7 (C9), 13.6 (C10).



2.126

3-(Benzofuran-2-yl)cyclopentanone (2.126). Adduct **2.126** was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/Et_2O (2:1) to yield 58 mg (96%) of **2.126** as a pale yellow oil. ^{1}H NMR (600 MHz) δ 7.50 (ddd, J = 7.6, 1.3, 0.7 Hz, 1 H), 7.42 (dd, J = 8.1, 0.9 Hz, 1 H), 7.24 (app td, J = 7.3, 1.5 Hz, 1 H), 7.20 (app td, J = 7.3, 1.0 Hz, 1 H), 6.45 (app t, J = 0.9 Hz, 1H), 3.67-3.61 (m, 1 H), 2.67 (dd, J = 18.2, 7.8 Hz, 1 H), 2.52 (ddd, J = 18.2, 9.0, 1.1 Hz, 1 H), 2.49-2.43 (comp, 2 H), 2.34-2.28 (m, 1 H), 2.26-2.19 (m, 1 H); ^{13}C NMR (150 MHz) δ 217.2, 159.5, 154.8, 128.4, 123.8, 122.7, 120.6, 110.9, 101.7, 43.3, 37.7, 35.8, 28.4; IR($CHCl_3$) 2965, 1741, 1455, 1253, 1166, 1136, 750 cm^{-1}; mass spectrum (CI) m/z 201.0916 ($C_{13}H_{13}O_2$ (M+1) requires 201.0916), 201(base). >98% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; 24.2 (Maj), 27.2.

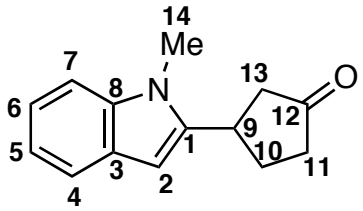
NMR ASSIGNMENTS: ^{1}H NMR (600 MHz) δ 7.50 (d, J = 7.6, 1 H, C7-H)), 7.42 (d, J = 8.1, 1 H, C4-H), 7.24 (app td, J = 8.1, 1.5 Hz, 1 H, C5-H), 7.20 (app td, J = 7.6, 1.0 Hz, 1 H, C6-H), 6.45 (app t, J = 0.9 Hz, 1H, C2-H), 3.67-3.61 (m, 1 H, C9-H), 2.67 (dd, J = 18.2, 7.8 Hz, 1 H, C13-H), 2.52 (ddd, J = 18.2, 9.0, 1.1 Hz, 1 H, C13-H), 2.49-2.43 (comp, 2 H, C11-H & C10-H), 2.34-2.28 (m, 1 H, C11-H), 2.26-2.19 (m, 1 H, C10-H); ^{13}C NMR (150 MHz) δ 217.2 (C12), 159.5 (C1), 154.8 (C8), 128.4 (C3), 123.8 (C5), 122.7 (C6), 120.6 (C7), 110.9 (C4), 101.7 (C2), 43.3 (C13), 37.7 (C11), 35.8 (C9), 28.4 (C10).



2.128

3-(Benzo[b]thiophen-2-yl)cyclopentanone (2.128). 2.128 was prepared according to method B. The residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1 to 1:1) to yield 49 mg (75%) of **2.128** as a brown solid; mp = 84.5–85.5°C. ^{1}H NMR (500 MHz) δ 7.78 (d, J = 7.9 Hz, 1 H), 7.69 (d, J = 7.5 Hz, 1 H), 7.33 (app td, J = 7.5, 1.2 Hz, 1 H), 7.29 (app td, J = 7.9, 1.3 Hz, 1 H), 7.08 (s, 1 H), 3.79-3.72 (m, 1 H), 2.77 (dd, J = 18.8, 7.5 Hz, 1 H), 2.59-2.45 (comp, 3 H), 2.37-2.29 (m, 1 H), 2.19-2.12 (m, 1 H); ^{13}C NMR (125 MHz) δ 216.9, 147.9, 139.7, 138.9, 124.4, 124.0, 123.1, 122.3, 119.8, 46.2, 38.4, 38.3, 31.6. IR ($CHCl_3$) 2963, 1736, 1436, 1399, 1171, 834, 771, 746, 728 cm^{-1}; mass spectrum (CI) m/z 217.0686 ($C_{13}H_{13}SO$ (M+1) requires 217.0687), 217 (base). 98% ee; OD-H Column, 98/2 Hexanes/i-PrOH,1 mL/min, rt; 27.2 (maj), 29.3.

NMR ASSIGNMENTS: ^{1}H NMR (500 MHz) δ 7.78 (d, J = 7.8 Hz, 1 H, C7-H), 7.69 (d, J = 7.5 Hz, 1 H, C4-H), 7.33 (app td, J = 7.5, 1.2 Hz, 1 H, C5-H), 7.29 (app td, J = 7.8, 1.3 Hz, 1 H, C6-H), 7.08 (s, 1 H, C2-H), 3.77 (m, 1 H, C9-H), 2.77 (dd, J = 18.8, 7.5 Hz, 1 H, C12-H), 2.59-2.45 (comp, 3 H, C13-H & C10-H), 2.37-2.29 (m, 1 H, C10-H), 2.19-2.12 (m, 1 H, C12-H); ^{13}C NMR (125 MHz) δ 216.9 (C11), 147.9 (C8), 139.7 (C1), 138.9 (C3), 124.4 (C5), 124.0 (C6), 123.1 (C4), 122.3 (C7), 119.8 (C2), 46.2 (C9), 38.4 (C10), 38.3 (C12), 31.6 (C13).

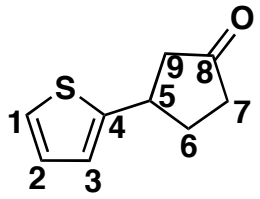


2.130

3-(1-Methyl-1*H*-indol-2-yl)cyclopentanone (2.130). Adduct **2.130** was prepared according to method A. (Note; after addition of the N-methylindol-2-yl titanate to the Michael acceptor (0.30 mmol), 10 mol % [Rh(acac)((*R*)-MeO-BIPHEP)] and $ClSiMe_3$ (49 mg, 0.45 mmol, 58 μL) in THF (1 mL) at –78 ˚C, the resultant mixture was stirred at –78 ˚C for 2 h, followed by stirring at room temperature until the starting material was consumed.) The residue was purified by flash chromatography, eluting with pentane/Et_2O (2:1) to yield 30 mg (47%) of **2.130** as a brown solid; mp = 124–125 ˚C; ^{1}H NMR (600 MHz) δ 7.55 (app dt, J = 7.9, 1.1 Hz, 1 H), 7.29 (dd, J = 8.2, 0.8 Hz, 1 H), 7.19 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H), 7.09 (ddd, J = 7.9, 7.0, 1.0 Hz, 1 H), 6.29 (app t, J = 0.8 Hz, 1 H), 3.74 (s, 3

H), 3.65-3.59 (m, 1 H), 2.72 (dd, J = 18.4, 7.9 Hz, 1 H), 2.52-2.43 (comp, 3 H), 2.37-2.27 (m, 1 H), 2.17-2.10 (m, 1 H); ^{13}C NMR (150 MHz) δ 217.5, 142.2, 137.8, 127.5, 121.4, 120.2, 119.7, 108.8, 97.7, 44.7, 37.5, 34.0, 29.8, 29.2; IR($CHCl_3$) 3050, 2960, 1740, 1467, 1400, 1313, 1232, 1169, 1153, 1133, 750 cm^{-1}; mass spectrum (CI) m/z 214.1228 ($C_{14}H_{16}NO$ (M+1) requires 214.1232), 214(base). 90% ee; AD Column, Hexanes/*i*-PrOH 95/5, 1.0 mL/min, rt; 14.4, 16.1 (Maj).

NMR ASSIGNMENTS: ^{1}H NMR (600 MHz) δ 7.55 (app dt, J = 7.9, 1.2 Hz, 1 H, C4-H), 7.29 (dd, J = 8.2, 0.8 Hz, 1 H, C7-H), 7.19 (ddd, J = 8.2, 7.0, 1.2 Hz, 1 H, C6-H), 7.09 (ddd, J = 7.9, 7.0, 0.8 Hz, 1 H, C5-H), 6.29 (app t, J = 0.8 Hz, 1 H, C2-H), 3.74 (s, 3 H, C14-H), 3.65-3.59 (m, 1 H, C9-H), 2.72 (dd, J = 18.4, 7.9 Hz, 1 H, C13-H), 2.52-2.43 (comp, 3 H, C13-H & C11-H & C10-H), 2.37-2.27 (m, 1H, C11-H), 2.17-2.10 (m, 1 H, C10-H); ^{13}C NMR (150 MHz) δ 217.5 (C12), 142.2 (C1), 137.8 (C8), 127.5 (C3), 121.4 (C6), 120.2 (C4), 119.7 (C5), 108.8 (C7), 97.7 (C2), 44.7 (C13), 37.5 (C11), 34.0 (C9), 29.8 (C14), 29.2 (C10).

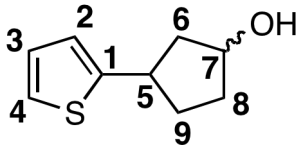


2.138

3-(Thiophen-2-yl)cyclopentanone (2.138). 2.138 was prepared according to method A. The residue was purified by flash chromatography, eluting with

pentane/Et_2O (5:1) to yield 30 mg (60%) of **2.138** as a colorless oil. ^1H NMR (600 MHz) δ 7.18 (dd, J = 5.1, 1.2 Hz, 1 H), 6.95 (dd, J = 5.1, 3.5 Hz, 1 H), 6.87 (app dt, J = 3.5, 1.2 Hz, 1 H), 3.71-3.65 (m, 1 H), 2.72 (dd, J = 18.1, 7.6 Hz, 1 H), 2.54-2.43 (comp, 2 H), 2.39 (ddd, J = 18.1, 10.3, 1.4 Hz, 1 H), 2.33-2.27 (m, 1 H), 2.09-2.02 (m, 1 H); ^{13}C NMR (150 MHz) δ 217.4, 147.4, 126.9, 123.5, 123.4, 46.8, 38.5, 37.6, 32.1; IR ($CHCl_3$) 2963, 1741, 1401, 1242, 1135, 913, 743, 699 cm^{-1}; mass spectrum (CI) m/z 167.0533 ($C_9H_{11}SO$ (M+1) requires 167.0531), 167(base). 95% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; First enantiomeric pair; 29.5 (Maj), 32.1; Second enantiomeric pair; 42.9, 54.5 (Maj).

NMR ASSIGNMENTS: ^1H NMR ($CDCl_3$, 600 MHz) δ 7.18 (dd, J = 5.1, 1.2 Hz, 1 H, C1-H), 6.95 (dd, J = 5.1, 3.5 Hz, 1 H, C2-H), 6.87 (app dt, J = 3.5, 1.2 Hz, 1 H, C3-H), 3.71-3.66 (m, 1 H, C5-H), 2.70 (dd, J = 18.1, 6.8 Hz, 1 H, C9-H), 2.53-2.51 (m, 1 H, C6-H), 2.46-2.41 (m, 1 H, C7-H), 2.39-2.27 (comp, 2 H, C7-H & C9-H), 2.09-2.02 (m, 1 H, C6-H); ^{13}C NMR (150 MHz) δ 217.4 (C8), 147.4 (C4), 126.9 (C1), 123.5 (C2), 123.4 (C3), 46.8 (C5), 38.5 (C9), 37.6 (C7), 32.1 (C6).

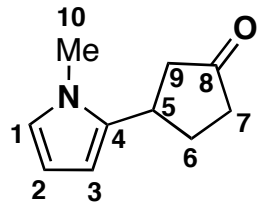


3-(Thiophen-2-yl)cyclopentanol (AJS-V-143). (Prepared for determination of enantiomeric excess of **2.138**). To a solution of compound **2.138** (46 mg, 0.28 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added sodium

borohydride (11 mg, 0.28 mmol) at 0 °C. After 30 minutes NH_4Cl (saturated aqueous, 2 mL) and CH_2Cl_2 (2 mL) were added to the reaction mixture. The layers were separated and the aqueous layers were extracted with Et_2O (3 x 1.5 mL). The combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with pentane/Et_2O (2:1) to furnish 47 mg (100%) of 3-(thiophen-2-yl)cyclopentanol as a mixture of cis/trans isomers (0.4:1) and as a colorless oil: ^{1}H NMR (500 MHz) in $CDCl_3$ δ 7.12 (dd, *J*= 4.0, 1.0 Hz, 1H), 7.11 (dd, *J*= 4.0, 1.0 Hz, 0.4 H), 6.92 (dd, *J*= 4.0, 3.0 Hz, 1.4 H), 6.84 (dt, *J* = 2.5, 1.0 Hz, 1 H), 6.81 (dt, *J* = 2.5, 1.0 Hz, 1 H), 4.51 (m, 0.4 H), 4.42 (m, 1 H), 3.65 (app p, *J*= 7.0 Hz, 0.4 H), 3.30 (app p, *J*= 7.0 Hz, 1 H), 2.56-2.51 (m, 1 H), 2.36-2.27 (m, 0.4 H), 2.22-2.09 (comp, 1.8 H), 1.99-1.55 (comp m, 5.2 H); ^{13}C NMR (125 MHz) in $CDCl_3$ δ 150.0, 126.6, 122.8, 122.7, 122.6, 73.4, 45.3, 44.9, 39.3, 38.4, 35.7, 35.4, 33.6, 33.4; IR 3339, 2956, 1439, 1340, 1080, 823 cm^{-1}; mass spectrum (CI) *m/z* 168.061 ($C_9H_{11}SO$ (M+1) requires 168.061), 168 (base); 95% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; First enantiomeric pair; 29.5 (Maj), 32.1; Second enantiomeric pair; 42.9, 54.5 (Maj).

NMR Assignments: ^{1}H NMR (500 MHz) in $CDCl_3$ δ 7.12 (dd, *J*= 4.0, 1.0 Hz, 1H, C4-H), 7.11 (dd, *J*= 4.0, 1.0 Hz, 0.4 H, C4-H), 6.92 (dd, *J*= 4.0, 3.0 Hz, 1.4 H, C3-H), 6.84 (dt, *J* = 2.5, 1.0 Hz, 1 H, C2-H), 6.81 (dt, *J* = 2.5, 1.0 Hz, 1 H, C2-H), 4.51 (m, 0.4 H, C7-H), 4.42 (m, 1 H, C7-H), 3.65 (app p, *J*= 7.0 Hz, 0.4 H, C5-H), 3.30 (app p, *J*= 7.0 Hz, 1 H, C5-H), 2.56-2.51 (m, 1 H, C6-H), 2.36-2.27 (m, 0.4 H, C6-H), 2.22-2.09 (comp, 1.8 H, C8-H & C6-H), 1.99-1.55

(comp m, 5.2 H, C8-H & C9-H); ^{13}C NMR (125 MHz) in $CDCl_3$ δ 150.0 (C1), 126.6 (C3), 122.8 (C2), 122.7 (C2), 122.6 (C4), 73.4 (C7), 45.3 (C6), 44.9 (C6), 39.3 (C8), 38.4 (C8), 35.7 (C5), 35.4 (C5), 33.6 (C9), 33.4 (C9).

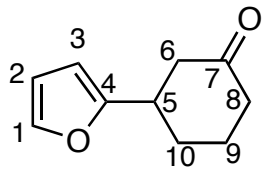


2.140

3-(1-Methyl-1H-pyrrol-2-yl)cyclopentanone (2.140). 2.140 was prepared according to method A. (Note; TESCl was used in place of TMSCl.) The residue was purified by flash chromatography, eluting with hexanes/EtOAc (4:1) to yield 21 mg (42%, 93% ee) of **2.140** as a brown oil. ^{1}H NMR (500 MHz) δ 6.59 (app t, J = 1.9 Hz, 1 H), 6.08 (dd, J = 3.4, 2.9 Hz, 1 H), 5.93 (ddd, J = 3.6, 1.7, 0.7 Hz, 1 H), 3.61 (s, 3 H), 3.45-3.38 (m, 1 H), 2.63 (dd, J = 18.3, 7.8 Hz, 1 H), 2.48-2.36 (comp, 2 H), 2.34-2.23 (comp, 2 H), 2.05-1.98 (m, 1 H); ^{13}C NMR (125 MHz) δ 218.2, 134.6, 122.2, 106.8, 104.4, 45.1, 37.9, 33.8, 33.8, 29.5. IR ($CHCl_3$) 2963, 1741, 1492, 1404, 1299, 1147, 1090, 713 cm^{-1}; mass spectrum (CI) m/z 164.1075 [$C_{10}H_{14}NO$ (M+1) requires 164.1075], 164 (base). 93% ee; OD-H Column, Hexanes/*i*-PrOH 96/4, 0.5 mL/min, rt; 49.2, 50.6 (Maj).

NMR ASSIGNMENTS: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.59 (m, 1 H, C1-H), 6.08 (dd, 3.4, 2.9 Hz, 1 H, C2-H), 5.93 (ddd, J = 3.4, 1.7, 0.7 Hz, 1 H, C3-H), 3.61 (s, 3 H, C10-H), 3.45-3.38 (m, 1 H, C5-H), 2.63 (dd, J = 18.3, 7.8 Hz, 1 H, C9-H), 2.48-2.36 (comp, 2 H, C7-H & C6-H), 2.34-2.23 (comp, 2 H, C9-H & C7-

H), 2.06-1.98 (m, 1 H, C6-H); ^{13}C NMR (125 MHz) δ 218.2, 134.6, 122.2, 106.8, 104.4, 45.1, 37.9, 33.8, 33.8, 29.5.

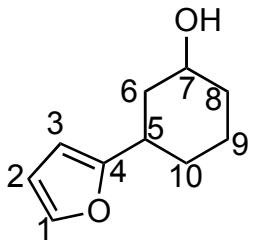


2.148

3-(Furan-2-yl)cyclohexanone (2.148). 2.148 was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to yield 30 mg (60%) of **2.148** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.32 (dd, J = 1.8, 0.8 Hz, 1 H), 6.29 (dd, J = 3.2, 1.8 Hz, 1 H), 6.02 (app dt, J = 3.2, 0.8 Hz, 1 H), 3.22–3.17 (m, 1 H), 2.68 (app ddt, J = 14.3, 4.8, 1.7 Hz, 1 H), 2.53 (ddd, J = 14.3, 10.6, 1.3 Hz, 1 H), 2.42 (app dtdd, J = 14.5, 5.1, 1.8, 1.2 Hz, 1 H), 2.34 (dddd, J = 14.5, 10.9, 5.8, 1.3 Hz , 1 H), 2.19–2.13 (m, 1 H). 2.06-1.99 (m, 1 H), 1.92-1.84 (m, 1 H), 1.82-1.73 (m, 1 H);^{13}C NMR (125 MHz) δ 210.1 , 157.2, 141.3, 110.1, 104.5, 45.6, 41.3, 37.6, 29.9, 24.4; IR ($CDCl_3$) 2944, 2866, 1711, 1505, 1224, 1010, 738 cm^{-1}; mass spectrum (CI) m/z 165.0915 [$C_{10}H_{13}O_2$ (M+1) requires 165.0916], 165 (base). 92% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 0.5 mL/min, rt; first enantiomeric pair; 30.2 (Maj), 33.1; second enantiomeric pair; 37.5 (Maj), 39.2.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.32 (dd, J = 1.8, 0.8 Hz, 1 H, C1-H), 6.29 (dd, J = 3.2, 1.8 Hz, 1 H, C2-H), 6.02 (dd, J = 3.2, 0.8 Hz, 1 H, C3-H), 3.22–3.17 (m, 1 H, C5-H), 2.68 (app ddt, J = 14.3, 4.7, 1.7 Hz, 1 H, C6-H), 2.53 (ddd, J = 14.3, 10.6, 1.3 Hz, 1 H, C6-H), 2.42 (app dt, J = 14.5, 5.1 Hz, 1 H,

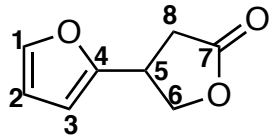
C8-H), 2.34 (dddd, *J* = 14.5, 10.8, 5.9, 1.3 Hz, 1 H, C8-H), 2.19–2.13 (m, 1 H, C10-H). 2.02 (m, 1 H, C9-H), 1.88 (dddd, *J* = 13.4, 10.8, 10.8, 3.5 Hz, 1 H, C10-H), 1.78 (ddddd, *J* = 13.8, 13.1, 10.8, 5.1, 3.5, 1 H, C9-H); ^{13}C NMR (125 MHz) δ 210.2 (C7), 157.2 (C4), 141.3 (C1), 110.1 (C2), 104.5 (C3), 45.6 (C6), 41.3 (C8), 37.6 (C5), 29.9 (C10), 24.4 (C9).



3-(Furan-2-yl)cyclohexanol (AJS-V-168). $NaBH_4$ (12 mg, 0.31 mmol) was added in one portion to a solution of furan **2.148** (51 mg, 0.31 mmol) in THF/MeOH (0.75mL/0.75mL) at 0 ˚C. The reaction was warmed to room temperature and stirred for an additional 1.5 h, whereupon H_2O (2 mL) was added. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (2:1 to 1:1) to yield 52 mg (100%) of 3-(furan-2-yl)cyclohexanol as a cis/trans mixture (8:1) and as a colorless oil: ^{1}H NMR (500 MHz) for the major diastereomer δ 7.30 (dd, *J* = 1.9, 0.7 Hz, 1 H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1 H), 5.97 (dt, *J* = 3.2, 0.7 Hz, 1 H), 3.70 (dddd, *J* = 11.0, 11.0, 4.2, 4.2 Hz, 1 H), 2.69 (dddd, *J* = 12.5, 12.5, 3.7, 3.7 Hz, 1 H), 2.32 (m, 1 H), 2.05–1.97 (comp, 2 H), 1.87 (m, 1 H), 1.46–1.33 (comp, 3 H), 1.29–1.20 (comp, 2 H); ^{13}C NMR (125 MHz) δ 159.4, 140.7, 109.9, 102.9, 70.4, 40.4, 35.9, 35.4, 30.6, 23.8; IR (CH_2Cl_2) 3343, 2934,

2859, 1505, 1450, 1362, 1054, 1010, 729, 598 cm^{-1}; mass spectrum (CI) *m/z* 166.0995 [$C_{10}H_{14}O_2$ (M+1) requires 166.0994], 166, 149 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.30 (dd, *J* = 1.9, 0.7 Hz, 1 H, C1-H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1 H, C2-H), 5.97 (dt, *J* = 3.2, 0.7 Hz, 1 H, C3-H), 3.70 (dddd, *J* = 11.0, 11.0, 4.2, 4.2 Hz, 1 H, C7-H), 2.69 (dddd, *J* = 12.5, 12.5, 3.7, 3.7 Hz, 1 H, C5-H), 2.32 (m, 1 H, C6-H), 2.05–1.97 (comp, 2 H, C10-H & C8-H), 1.87 (m, 1 H, C9-H), 1.46–1.33 (comp, 3 H, OH, C10-H & C6-H), 1.29–1.20 (comp, 2 H, C8-H & C9-H); ^{13}C NMR (125 MHz) *δ* 159.4 (C4), 140.7 (C1), 109.9 (C2), 102.9 (C3), 70.4 (C7), 40.4 (C5), 35.9 (C6), 35.4 (C8), 30.6 (C10), 23.8 (C9).

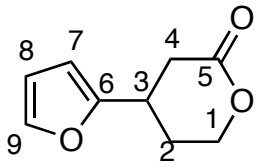


2.149

4-(Furan-2-yl)-dihydrofuran-2(3*H*)-one (2.149). 2.149 was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1 to 2:1) to yield 27 mg (55%) of **2.149** as a colorless oil. ^{1}H NMR (600 MHz) *δ* 7.37 (dd, *J* = 1.9, 0.8 Hz, 1 H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1 H), 6.17 (app dt, *J* = 3.2, 0.8 Hz, 1 H), 4.57 (dd, *J* = 9.0, 7.8 Hz, 1 H), 4.34 (dd, *J* = 9.0, 7.3 Hz, 1 H), 3.85 (app pentet, *J* = 8.2 Hz, 1 H), 2.84 (dd, *J* = 17.5, 8.7 Hz, 1 H), 2.76 (dd, *J* = 17.5, 8.4 Hz, 1 H); ^{13}C NMR (150 MHz) *δ* 175.7, 152.2, 142.5, 110.4, 106.3, 71.5, 34.9, 33.4; IR ($CDCl_3$) 3539, 3121, 2975, 2915, 1778, 1507, 1480, 1422, 1373, 1335, 1171, 1012, 741 cm^{-1}; mass spectrum

(CI) *m/z* 153.0555 ($C_8H_9O_3$ (M+1) requires 153.0552), 153 (base). >98% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; 29.3 (Maj), no other isomer detected.

NMR Assignments: ^{1}H NMR (600 MHz) δ 7.37 (dd, J = 1.9, 0.8 Hz, 1 H, C1-H), 6.33 (dd, J = 3.2, 1.9 Hz, 1 H, C2-H), 6.17 (app dt, J = 3.2, 0.8 Hz, 1 H, C3-H), 4.57 (dd, J = 9.0, 7.8 Hz, 1 H, C6-H), 4.34 (dd, J = 9.0, 7.3 Hz, 1 H, C6-H), 3.85 (app pentet, J = 8.2 Hz, 1 H, C5-H), 2.84 (dd, J = 17.5, 8.7 Hz, 1 H, C8-H), 2.76 (dd, J = 17.5, 8.4 Hz, 1 H, C8-H); ^{13}C NMR (150 MHz) δ 175.7 (C7), 152.2 (C4), 142.5 (C1), 110.4 (C3), 106.3 (C2), 71.5 (C6), 34.9 (C5), 33.4 (C8).

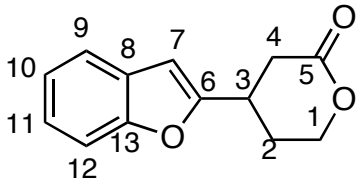


2.150

4-(Furan-2-yl)tetrahydro-2*H*-pyran-2-one (2.150). 2.150 was prepared according to method A. The residue was purified by flash chromatography, eluting with pentane/EtOAc (2:1) to yield 21 mg (42%) of **2.150** as a colorless oil; ^{1}H NMR (500 MHz) δ 7.36 (dd, J = 1.7, 0.7 Hz, 1 H), 6.32 (dd, J = 3.2, 1.7 Hz, 1 H), 6.09 (app dt, J = 3.2, 0.7 Hz, 1 H), 4.42 (ddd, J = 11.5, 5.6, 4.6 Hz, 1 H), 4.36 (ddd, J = 11.5, 8.8, 4.1 Hz, 1 H), 3.40–3.34 (m, 1 H), 2.93 (ddd, J = 17.6, 6.3, 1.2 Hz, 1 H), 2.72 (dd, J = 17.6, 9.3 Hz, 1 H), 2.27–2.21 (m, 1 H), 2.08–2.01 (m, 1 H); ^{13}C NMR (125 MHz) δ 170.0, 155.4, 142.0, 110.2, 105.1, 67.9, 34.5, 31.0, 27.8; IR($CHCl_3$) 2966, 2912, 1736, 1507, 1405, 1255, 1221, 1073, 1013, 741, 599

cm^{-1}; mass spectrum (CI) *m/z* 167.0707 ($C_9H_{11}O_3$ (M+1) requires 167.0708), 167 (base). 97% ee; OD-H Column, Hexanes/*i*-PrOH 98/2, 1.0 mL/min, rt; 51.3, 52.7 (Maj).

NMR Assignments: ^{1}H NMR (600 MHz) δ 7.36 (dd, *J* = 1.7, 0.7 Hz, 1 H, C9-H), 6.32 (dd, *J* = 3.2, 1.7 Hz, 1 H, C8-H), 6.09 (app td, *J* = 3.2, 0.7 Hz, 1 H, C7-H), 4.42 (ddd, *J* = 11.5, 5.6, 4.6 Hz, 1 H, C1-H), 4.36 (ddd, *J* = 11.5, 8.8, 4.1 Hz, 1 H, C1-H), 3.40–3.34 (m, 1 H, C3-H), 2.93 (ddd, *J* = 17.6, 6.3, 1.2 Hz, 1 H, C4-H), 2.72 (dd, *J* = 17.6, 9.3 Hz, 1 H, C4-H), 2.27–2.21 (m, 1 H, C2-H), 2.08–2.01 (m, 1 H, C2-H); ^{13}C NMR (150 MHz) δ 170.0 (C5), 155.4 (C6), 142.0 (C9), 110.2 (C8), 105.1 (C7), 67.9 (C1), 34.5 (C4), 31.0 (C3), 27.8 (C2).

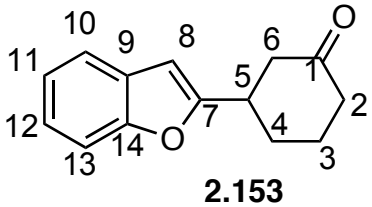


2.151

4-(Benzofuran-2-yl)tetrahydro-2*H*-pyran-2-one (2.151). Adduct **2.151** was prepared according to method A. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to yield 46 mg (70%) of **2.151** as a white solid; mp = 95–96 °C; ^{1}H NMR (500 MHz) δ 7.52 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1 H), 7.43 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.26 (app td, *J* = 8.1, 1.4 Hz, 1 H), 7.22 (app td, *J* = 7.7, 1.0 Hz, 1 H), 6.45 (app t, *J* = 1.0 Hz, 1H), 4.48 (ddd, *J* = 11.5, 5.7, 4.6 Hz, 1 H), 4.41 (ddd, *J* = 11.5, 8.8, 4.0 Hz, 1 H), 3.54–3.49 (m, 1 H),

3.01 (ddd, J = 17.5, 6.3, 1.2 Hz, 1 H), 2.84 (dd, J = 17.5, 9.2 Hz, 1 H), 2.36–2.31 (m, 1 H), 2.17 (dddd, J = 13.5, 8.8, 8.8, 4.6 Hz, 1 H); ^{13}C NMR (150 MHz) δ 169.7, 158.2, 154.8, 128.1, 124.2, 122.9, 120.8, 111.0, 102.2, 67.9, 34.2, 31.4, 27.6; IR($CHCl_3$) 2960, 2920, 1734, 1455, 1253, 1074, 753 cm^{-1}; mass spectrum (CI) m/z 217.0859 ($C_{13}H_{13}O_3$ (M+1) requires 217.0862), 217, 164(base), 120. >98% ee; OD-H Column, Hexanes/i-PrOH 2/1, 0.8 mL/min, rt; 46.2 (Maj). No minor isomer detected.

NMR Assignments: ^{1}H NMR (600 MHz) δ 7.52 (d, J = 7.7 Hz, 1 H, C9-H), 7.43 (d, J = 7.3 Hz, 1 H, C12-H), 7.26 (app td, J = 7.3, 1.3 Hz, 1 H, C11-H), 7.23 (app td, J = 7.7, 1.0 Hz, 1 H, C10-H), 6.45 (s, 1H, C7-H), 4.48 (ddd, J = 11.5, 5.7, 4.6 Hz, 1 H, C1-H), 4.41 (ddd, J = 11.5, 8.8, 4.0 Hz, 1 H, C1-H), 3.54–3.49 (m, 1 H, C3-H), 3.01 (ddd, J = 17.5, 6.2, 1.2 Hz, 1 H, C4-H), 2.84 (dd, J = 17.5, 9.1 Hz, 1 H, C4-H), 2.36–2.31 (m, 1 H, C2-H), 2.17 (dddd, J = 13.5, 8.8, 8.8, 4.6 Hz, 1 H, C2-H); ^{13}C NMR (150 MHz) δ 169.7 (C5), 158.2 (C6), 154.8 (C13), 128.1 (C8), 124.2 (C11), 122.9 (C10), 120.8 (C9), 111.0 (C12), 102.2 (C7), 67.9 (C1), 34.2 (C4), 31.4 (C3), 27.6 (C2).

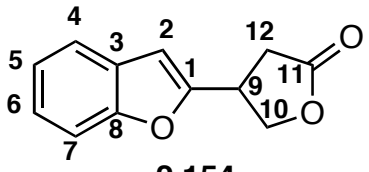


2.153

3-(Benzofuran-2-yl)cyclohexanone (2.153). 2.153 was prepared according to method B. The residue was purified by flash chromatography,

eluting with pentane/Et_2O (2:1) to yield 60 mg (93%) of **2.153** as a colorless oil. ^{1}H NMR (500 MHz) δ 7.50 (ddd, J = 7.6, 1.4, 0.7 Hz, 1 H), 7.42 (ddd, J = 8.0, 1.7, 1.0 Hz, 1 H), 7.24 (ddd, J = 8.0, 7.3, 1.4 Hz, 1 H), 7.19 (app td, J = 7.6, 1.3 Hz, 1 H), 6.42 (app t, J = 1.0 Hz, 1 H), 3.37-3.31 (m, 1 H), 2.77 (app ddt, J = 14.4, 4.8, 1.6 Hz, 1 H), 2.66 (ddd, J = 14.4, 10.4, 1.3 Hz, 1 H), 2.46 (app dt, J = 14.6, 5.2, 1 H), 2.39 (dddd, J = 14.6, 10.6, 5.8, 1.3, 1 H), 2.28–2.23 (m, 1 H), 2.10–1.98 (comp, 2 H), 1.87–1.79 (m, 1 H); ^{13}C NMR (125 MHz) δ 209.8, 159.9, 154.6, 128.4, 123.7, 122.7, 120.6, 110.9, 101.7, 45.3, 41.3, 37.9, 29.7, 24.4. IR ($CHCl_3$) 2945, 2865, 1713, 1454, 1254, 1169, 752, cm^{-1}; mass spectrum (CI) m/z 215.1077 ($C_{14}H_{15}O_2$ (M+1) requires 215.1072), 215 (base). 90% ee; OD-H Column, 90/10 Hexanes/i-PrOH, 0.5 mL/min, rt; 35.2, 36.2 (Maj).

NMR ASSIGNMENTS: ^{1}H NMR (500 MHz) δ 7.50 (ddd, J = 7.6, 1.4, 0.7 Hz, 1 H), 7.42 (ddd, J = 8.0, 1.7, 1.0 Hz, 1 H), 7.24 (ddd, J = 8.0, 7.3, 1.4 Hz, 1 H), 7.19 (ddd, J = 7.6, 7.3, 1.0 Hz, 1 H), 6.42 (app t, J = 1.0 Hz, 1 H, C8-H), 3.37–3.31 (m, 1 H, C5-H), 2.77 (app ddt, J = 14.4, 4.8, 1.6 Hz, 1 H, C6-H), 2.66 (ddd, J = 14.4, 10.4, 1.3 1.0 Hz, 1 H, C6-H), 2.46 (app dt, J = 14.6, 5.2, 1 H, C2-H), 2.39 (dddd, J = 10.6, 7.1, 5.8, 1.2, 1 H, C3-H), 2.28–2.23 (m, 1 H, C2-H), 2.10–2.01 (comp, 2 H, C3-H & C4-H), 1.87–1.79 (m, 1 H, C4-H); ^{13}C NMR (125 MHz) δ 209.8 (C1), 159.9 (C7), 154.6 (C14), 128.4 (C9), 123.7 (C10), 122.7 (C13), 120.6 (C12), 110.9 (C11), 101.7 (C8), 45.3 (C6), 41.3 (C2), 37.9 (C5), 29.7 (C4), 24.4 (C3).

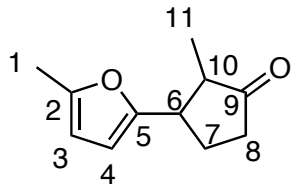


2.154

4-(Benzofuran-2-yl)-dihydrofuran-2(3*H*)-one (2.154). 2.154 was prepared according to method B. The residue was purified by flash chromatography, eluting with hexanes/EtOAc (3:1) to yield 39 mg (64%) of **3.154** as a yellow solid; mp = 80–81 °C; ^{1}H NMR (600 MHz) δ 7.52 (ddd, J = 7.7, 1.3, 0.7 Hz, 1 H), 7.44 (ddd, J = 8.3, 1.7, 0.9 Hz, 1 H), 7.28 (app td, J = 7.3, 1.3 Hz, 1 H), 7.23 (app td, J = 7.7, 1.0 Hz, 1 H), 6.57 (app t, J = 0.9, 1 H), 4.65 (dd, J = 9.1, 7.9 Hz, 1H), 4.47 (dd, J = 9.1, 7.2 Hz, 1H) 4.01–3.96 (m, 1 H), 2.94 (dd, J = 17.5, 8.8 Hz, 1 H), 2.89 (dd, J = 17.5, 8.2 Hz, 1 H); ^{13}C NMR (150 MHz) δ 175.4, 155.0, 154.9, 127.9, 124.5, 123.1, 120.9, 111.1, 103.4, 71.1, 35.3, 33.1; IR($CHCl_3$) 2917, 1781, 1455, 1254, 1172, 1026, 753 cm^{-1}; mass spectrum (CI) m/z 203.0703 ($C_{12}H_{11}O_3$ (M+1) requires 203.0707), 203(base). >98% ee; OD-H Column, Hexanes/*i*-PrOH 90/10, 1.0 mL/min, rt; 36.0, 40.3 (Maj).

^{1}H NMR (600 MHz) δ 7.52 (ddd, J = 7.7, 1.3, 0.7 Hz, 1 H, C4-H), 7.44 (ddd, J = 8.3, 1.7, 0.9 Hz, 1 H, C7-H), 7.28 (app td, J = 7.3, 1.3 Hz, 1 H, C6-H), 7.23 (app td, J = 7.7, 1.0 Hz, 1 H, C5-H), 6.57 (app t, J = 0.9, 1 H, C2-H), 4.65 (dd, J = 9.1, 7.9 Hz, 1H, C10-H), 4.47 (dd, J = 9.1, 7.2 Hz, 1H, C10-H) 4.01–3.96 (m, 1 H, C9-H), 2.94 (dd, J = 17.5, 8.8 Hz, 1 H, C12-H), 2.89 (dd, J = 17.5, 8.2 Hz, 1 H, C12-H); ^{13}C NMR (150 MHz) δ 175.4 (C11), 155.0 (C1), 154.9 (C8), 127.9 (C3), 124.5 (C5), 123.1 (C6), 120.9 (C4), 111.1 (C7), 103.4 (C2), 71.1 (C10), 35.3 (C12), 33.1 (C9).

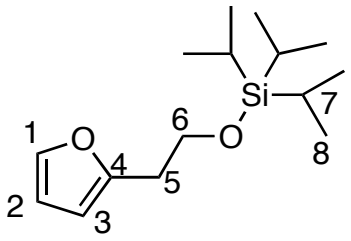
4.4 STUDIES TOWARDS THE TOTAL SYNTHESIS OF CORTISTATIN A



3.159

2-Methyl-3-(5-methylfuran-2-yl)cyclopentanone (3.159). (AJS-IV-112). Tetrabutylammonium trifluorodiphenylsilicate (151 mg in CH_2Cl_2, 3 mL) was added via cannula to a solution of Et_3N (67 mg, 0.67 mmol, 92μL) and **3.161** (50 mg, 0.19 mmol) in PhMe (3 mL) at rt. The resultant mixture was stirred at rt for 24 h. 1 N aqueous HCl (2 mL) was added, and the resultant mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (1:1) to yield 19 mg (58%) of **3.159** as a colorless oil: ^{1}H NMR (500 MHz) δ 5.96 (d, J = 2.9 Hz, 1 H), 5.89 (dd, J = 2.9, 1.0 Hz, 1 H), 2.86 (td, J = 11.5, 5.9 Hz, 1 H), 2.48 (dd, J = 9.4, 18.8 Hz, 1 H), 2.34-2.17 (comp, 7 H), 2.05-1.95 (comp, 1 H), 1.13 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 219.7, 154.6, 151.3, 106.1, 105.8, 49.6, 44.1, 37.5, 26.9, 13.8, 13.0; IR ($CDCl_3$) 2964, 2874, 1742, 1568, 1454, 1407, 1217, 1160, 1021, 783 cm^{-1}; mass spectrum (CI) m/z 179.1077 [$C_{18}H_{20}O_3$ (M+1) requires 179.1072], 179 (base), 192, 207.

NMR Assignments: ^{1}H NMR (500 MHz) δ 5.96 (d, J = 2.9 Hz, 1 H, C4-H), 5.89 (dd, J = 2.9, 1.0 Hz, 1 H, C3-H), 2.86 (td, J = 11.5, 11.5, 5.9 Hz, 1 H, C6-H), 2.48 (dd, J = 9.4, 18.8 Hz, 1 H, C8-H), 2.34-2.17 (comp, 4 H, C7-H, C8-H, C10-H), 2.27 (s, 3 H, C1-H) 2.05-1.95 (comp, 1 H, C7-H), 1.13 (d, J = 7.0 Hz, 3 H, C11-H); ^{13}C NMR (125 MHz) δ 219.7 (C9), 154.6 (C2), 151.3 (C5), 106.1 (C3), 105.8 (C4), 49.6 (C8), 44.1 (C10), 37.5 (C6), 26.9 (C7), 13.8 (C1), 13.0 (C11).

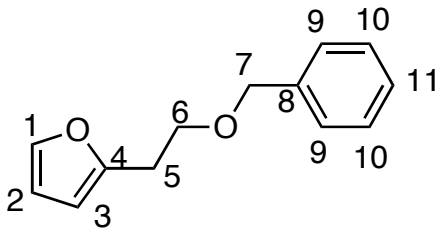


3.163

(2-(Furan-2-yl)ethoxyl)triisopropylsilane (3.163). (AJS-III-103). 2-furylethanol **3.162** (500 mg, 4.5 mmol) was added to a solution of imidazole (769 mg, 11.3 mmol, 2.5 eq) and chlorotriisopropylsilane (1.14 g, 5.9 mmol, 1.3 eq) in DMF (50 mL) at 0 ˚C. The resultant mixture was stirred at 0 ˚C for 30 min. The cold bath was removed, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was washed with 1 N HCl (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 904 mg (80%) of **3.163** as a colorless oil: ^{1}H NMR (500 MHz) δ 7.30 (dd, J = 1.8, 0.9 Hz, 1 H), 6.28 (dd, J = 3.1, 1.8 Hz, 1 H), 6.06

(dd, J = 3.1, 0.9 Hz, 1 H), 3.92 (t, J = 7.0 Hz, 2 H), 2.88 (t, J = 7.0 Hz, 2 H), 1.09–1.02 (m, 21 H); ^{13}C NMR (125 MHz) δ 153.4, 140.9, 110.2, 106.0, 62.0, 32.1, 17.9, 11.9. IR ($CDCl_3$) 2942, 2866, 1463, 1109, 883, 728, 681 cm^{-1}; mass spectrum (CI) m/z 269.1942 [$C_{15}H_{29}O_2Si$ (M+1) requires 269.1937], 225, 269 (base), 271 (base).

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.30 (dd, J = 1.8, 0.9 Hz, 1 H, C1-H), 6.28 (dd, J = 3.1, 1.8 Hz, 1 H, C2-H), 6.06 (dd, J = 3.1, 0.9 Hz, 1 H, C3-H), 3.92 (t, J = 7.0 Hz, 2 H, C6-H), 2.88 (t, J = 7.0 Hz, 2 H, C5-H), 1.09–1.02 (m, 21 H, C7-H & C8-H); ^{13}C NMR (125 MHz) δ 153.4 (C4), 140.9 (C1), 110.2 (C2), 106.0 (C3), 62.0 (C6), 32.1 (C5), 17.9 (C8), 11.9 (C7).

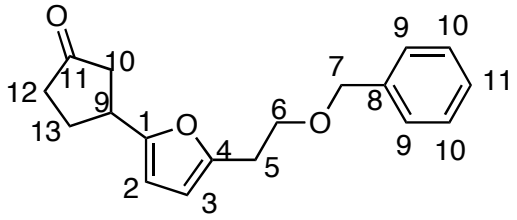


3.164

2-(2-(Benzyloxy)ethyl)furan (3.164). (AJS-III-100). Benzyl bromide (168 mg, 117 μL, 0.98) was added to a solution of sodium hydride (39 mg, 0.98 mmol, 60% wt. in mineral oil) and **3.162** (100 mg, 0.89 mmol) in DMF (3 mL) at 0 ˚C. The resultant mixture was warmed to room temperature over 2 h and then stirred for an additional 12 h at room temperature. Saturated aqueous NH_4Cl (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash

chromatography, eluting with pentane/Et_2O (4:1) to yield 117 mg (65%) of **3.164** as a colorless oil: ^{1}H NMR (500 MHz) δ 7.35–7.26 (m, 6 H), 6.30 (dd, J = 3.1, 1.8 Hz, 1 H), 6.07 (dd, J = 3.1, 0.8 Hz, 1 H), 4.53 (s, 2 H), 3.73 (t, J = 7.0 Hz, 2 H), 2.95 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (125 MHz) δ 153.1, 141.1, 138.3, 128.4, 127.6, 127.5, 110.2, 105.9, 72.9, 68.3, 28.9; IR ($CDCl_3$) 3030, 2909, 2860, 1598, 1506, 1454, 1363, 1178, 1103, 1007, 802, 734, 698, 600 cm^{-1}; mass spectrum (CI) m/z 203.1077 [$C_{13}H_{15}O_2$ (M+1) requires 203.1072], 185, 203 (base), 293.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.35–7.26 (m, 5 H, Ph-H & C1-H), 6.30 (dd, J = 3.1, 1.8 Hz, 1 H, C2-H), 6.07 (dd, J = 3.1, 0.8 Hz, 1 H, C3-H), 4.53 (s, 2 H, C7-H), 3.73 (t, J = 7.0 Hz, 2 H, C6-H), 2.95 (t, J = 7.0 Hz, 2 H, C5-H); ^{13}C NMR (125 MHz) δ 153.1 (C4), 141.1 (C1), 138.3 (C8), 128.4 (C9), 127.6 (C10), 127.5 (C11), 110.2 (C2), 105.9 (C3), 72.9 (C7), 68.3 (C6), 28.9 (C5).



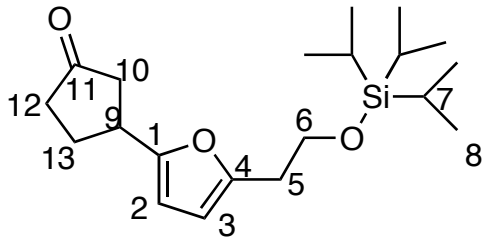
3.168

3-(5-(2-(Benzyloxy)ethyl)furan-2-yl)cyclopentanone (3.168). (AJS-III-102). *sec*-BuLi (1.4 M in cyclohexane/hexane, 70 μL, 0.10 mmol) was added to a solution of **3.164** (20 mg, 0.10 mmol) in THF (400 μL) at –78 ˚C. The resultant solution was warmed from –78 ˚C to 0 ˚C over 2 h and then transferred via

cannula to a vial charged with fused $ZnCl_2$ (20 mg, 0.15 mmol) at 0 ˚C. The resultant mixture was stirred for 30 min and then added to a solution of cyclopentenone (6 mg, 0.075 mmol, 6 μL), 10 mol % $[RhCl((S)\text{-binap})]_2$ (generated *in situ* from $[Rh(cod)Cl]_2$ and (*S*)-BINAP), and $ClSiMe_3$ (16 mg, 0.15 mmol, 19 μL) in THF (400 μL). The mixture was stirred at room temperature for 12 h. Aqueous HCl (0.5 N, 2.0 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1) to yield 10 mg (42%) of **3.168** as a colorless oil: ^{1}H NMR (500 MHz) δ 7.37-7.26 (m, 5 H), 5.97 (d, J = 3.1 Hz, 1 H), 5.95 (dd, J = 3.1, 0.7 Hz, 1 H), 4.54 (s, 2H), 3.71 (t, J = 6.9 Hz. 2 H), 3.48-3.41 (m, 1 H), 2.91 (t, J = 6.9 Hz, 2 H), 2.55 (dd, J = 18.6, 7.8 Hz, 1 H), 2.41-2.31 (m, 3 H), 2.27-2.21 (m, 1 H), 2.12-2.04 (m, 1 H) ; ^{13}C NMR (125 MHz) δ 217.9, 155.1, 152.1, 138.3, 128.6, 128.4, 127.6, 126.9, 106.4, 105.2, 72.9, 68.3, 43.6, 37.7, 35.5, 28.9, 28.6; IR ($CDCl_3$) 2943, 2866, 1745, 1463, 1107, 1013, 882, 818, 739, 679 cm^{-1}; mass spectrum (CI) [$C_{18}H_{20}O_3$ (M+1) requires 285], 163, 177, 207, 267 (base), 285.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.37-7.26 (m, 5 H, Ph-H), 5.97 (d, J = 3.1 Hz, 1 H, C2-H)), 5.95 (dd, J = 3.1, 0.7 Hz, 1 H, C3-H)), 4.54 (s, 2H, C7-H), 3.71 (t, J = 6.9 Hz, 2 H, C6-H), 3.48-3.41 (m, 1 H, C9-H), 2.91 (t, J = 6.9 Hz, 2 H, C5-H), 2.55 (dd, J = 18.6, 7.8 Hz, 1 H, C10-H), 2.41-2.31 (m, 3 H, C10-H, C12-H, & C13-H)), 2.27-2.21 (m, 1 H, C12-H), 2.12-2.04 (m, 1 H, C13-H) ; ^{13}C NMR (125 MHz) δ 217.9 (C11), 155.1 (C1), 152.1 (C4), 138.3 (C8),

128.4 (C10), 127.6 (C9), 126.9 (C11), 106.4 (C2), 105.2 (C3), 72.9 (C7), 68.3 (C6), 43.6 (C10), 37.7 (C12), 35.5 (C9), 28.9 (C5), 28.6 (C13).

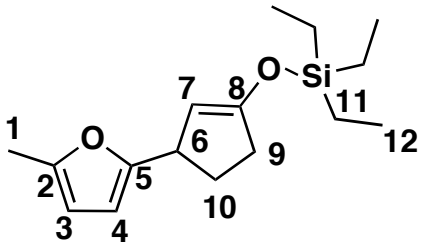


3.169

2-(2-triisopropylsiloxyethyl)-5-(3-cylopentanone)furan (3.169). (AJS-III-104). *sec*-BuLi (1.4 M in cyclohexane/hexane, 214 μL, 0.30 mmol) was added to a solution of **3.163** (100 mg, 0.37 mmol) in anhydrous THF (2 mL) at –78 ˚C. The resultant solution was slowly warmed from –78 ˚C to 0 ˚C over 2 h and then transferred via cannula to a vial charged with fused $ZnCl_2$ (50 mg, 0.37 mmol) at 0 ˚C. The resultant mixture was stirred for 30 min, and the solution was added to a solution of cyclopentenone (12 mg, 0.15 mmol, 12 μL), 10 mol % $[RhCl((S)\text{-binap})]_2$ (generated *in situ* from $[Rh(cod)Cl]_2$ and (*S*)-BINAP), and $ClSiMe_3$ (25 mg, 0.23 mmol, 29 μL) in THF (2 mL). The mixture was stirred at room temperature for 14 h. Aqueous HCl (0.5 N, 2.0 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (3:1) to yield 44 mg (80%) of **3.169** as a colorless oil: ^{1}H NMR (500 MHz) δ 5.97 (d, J = 3.0 Hz, 1 H), 5.94 (dd, J = 3.0, 0.9 Hz, 1 H), 3.91 (t, J = 6.9

Hz, 2 H), 3.47-3.41 (m, 1 H), 2.83 (t, J = 6.9 Hz, 2 H), 2.55 (dd, J = 18.5, 7.8 Hz, 1 H), 2.41-2.31 (comp, 3 H), 2.27-2.22 (comp, 1 H), 2.12-2.04 (comp, 1 H), 1.10-1.01 (comp, 21 H); ^{13}C NMR (125 MHz) δ 218.0, 154.9, 152.5, 106.6, 105.1, 61.9, 43.6, 37.8, 35.5, 32.1, 28.6, 17.9, 11.9; IR ($CDCl_3$) 2943, 2866, 1745, 1463, 1107, 1013, 882, 818, 739, 679 cm^{-1}; mass spectrum (CI) m/z 353.2505 [$C_{20}H_{37}O_3Si$ (M+1) requires 353.2512], 179, 310, 335, 353 (base), 355.

NMR Assignments: ^{1}H NMR (500 MHz) δ 5.97 (d, J = 3.0 Hz, 1 H, C2-H), 5.94(dd, J = 3.0, 0.9 Hz, 1 H, C3-H), 3.91 (t, J = 6.9 Hz, 2 H, C6-H), 3.47-3.41 (m, 1 H, C9-H), 2.83 (t, J = 6.9 Hz, 2 H, C5-H), 2.55 (dd, J = 18.5, 7.8 Hz, 1 H, C10-H), 2.41-2.31 (comp, 3 H, C10-H, C12-H, C13-H), 2.27-2.22 (comp, 1 H, C12-H)), 2.12-2.04 (comp, 1 H, C13-H), 1.10-1.01 (comp, 21 H, C7-H & C8-H); ^{13}C NMR (125 MHz) δ 218.0 (C11), 154.9 (C1), 152.5 (C4), 106.6 (C3), 105.1 (C2), 61.9 (C6), 43.6 (C10), 37.8 (C12), 35.5 (C9), 32.1 (C5), 28.6 (C13), 17.9 (C8), 11.9 (C7).

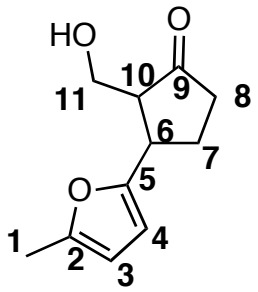


3.161

(3-(5-methylfuran-2-yl)cyclopent-1-enyloxy)triethylsilane (AJS-IV-35) (3.161). Furyltitanate **2.116** (0.34 M in THF/cyclohexane/hexane, 2.3 mL, 0.79 mmol) was added to a solution of cyclopentenone (50 mg, 0.61 mmol, 51 μL), $ClSiEt_3$ (138 mg, 0.92 mmol, 154 μL), and 10 mol % $[RhCl((rac)\text{-Binap})]_2$ (generated *in situ* from $[Rh(cod)Cl]_2$ and (*rac*)-BINAP) in THF (2.0 mL). The

resultant mixture was stirred at room temperature for 12 h and then transferred via cannula to a suspension of celite (5 g) in saturated aqueous $NaHCO_3$ (10.0 mL). The biphasic mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and the residue was purified by flash chromatography (neutral Al_2O_3), eluting with pentane to yield 162 mg (95 %) of **3.161** as a colorless oil. ^{1}H NMR (400 MHz) δ 5.83-5.81 (comp, 2 H), 4.70 (app dt, J = 2.0, 1.6 Hz, 1 H), 3.82 (m, 1 H), 2.45-2.20 (comp, 7 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.70 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz) δ 158.7, 156.9, 150.5, 105.9, 104.1, 103.6, 40.9, 33.1, 28.7, 13.8, 6.8, 5.0; IR (neat) 2955, 2877, 1742, 1644, 1459, 1342, 1248, 1073, 1018 cm^{-1}; mass spectrum (CI) *m/z* 279.1777 [$C_{18}H_{20}O_3$ (M+1) requires 279.1780], 279 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.83-5.81 (comp, 2 H, C3-H & C4-H), 4.70 (app dt, J = 2.0, 1.6, 1 H, C7-H), 3.85-3.80 (m, 1 H, C6-H), 2.45-2.20 (comp, 7 H, C1-H & C10-H & C9-H), 0.98 (t, J = 8.0 Hz, 9 H, C12-H), 0.70 (q, J = 8.0 Hz, 6 H, C11-H); ^{13}C NMR (125 MHz) δ 158.7 (C8), 156.9 (C5), 150.5 (C2), 105.9 (C4), 104.1 (C3), 103.6 (C7), 40.9 (C6), 33.1 (C9), 28.7 (C10), 13.8 (C1), 6.8 (C11), 5.0 (C12).

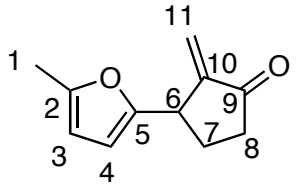


3.184

2-(Hydroxymethyl)-3-(5-methylfuran-2-yl)cyclopentanone (3.184). (AJS-IV-40). Silyl enol ether **3.161** (20 mg, 0.07 mmol) was added to a solution of samarium(III) triflate (84 mg, 0.14 mmol) and formaldehyde (100 μL, 40% wt. in H_2O) in THF (300 μL). The resultant mixture was stirred at room temperature for 24 h, and CH_2Cl_2 (2 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed with brine (1 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (1:1) to yield 6 mg (44%) of **3.181** as a colorless oil. ^{1}H NMR (400 MHz) δ 5.99 (d, J = 3.2 Hz, 1 H), 5.88 (dd, J = 3.2, 0.8 Hz, 1 H), 3.96 (ddd, J = 11.2, 7.2, 4.4 Hz, 1 H), 3.75 (dt, J = 11.2, 5.6 Hz, 1 H), 3.26 (td, J = 11.2, 6.8 Hz, 1 H), 2.54-2.21 (comp, 8 H), 2.10-2.09 (m, 3 H); ^{13}C NMR (125 MHz) δ 219.7, 153.6, 151.3, 105.9, 105.9, 60.2, 55.9, 38.1, 37.8, 26.6, 13.5; IR (neat) 3456, 2922, 2881, 1740, 1218, 1022, 785 cm^{-1}.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.99 (d, J = 3.2 Hz, 1 H, C3-H), 5.88 (dd, J = 3.2, 0.8 Hz, 1 H, C4-H), 3.96 (ddd, J = 11.2, 7.2, 4.4 Hz, 1 H, C11-H), 3.75 (dt, J = 11.2, 5.6 Hz, 1 H, C11-H), 3.26 (td, J = 11.6, 6.0 Hz, 1 H,

C6-H), 2.54-2.21 (comp, 8 H, C10-H & C9-H & C7-H & C1-H), 2.10-2.09 (m, 1 H, OH); ^{13}C NMR (125 MHz) δ 219.7 (C9), 153.6 (C2), 151.3 (C5), 105.9 (C3), 105.9 (C4), 60.2 (C11), 55.9 (C6), 38.1 (C10), 37.8 (C8), 26.6 (C7), 13.5 (C1).

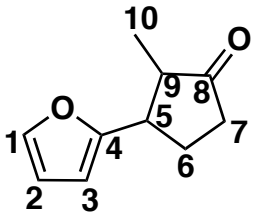


3.187

2-Methylene-3-(5-methylfuran-2-yl)cyclopentanone (3.187) (AJS-IV-50). Methanesulfonylchloride (6.4 mg, 0.06 mmol, 5 μL) and *N*,*N*-diisopropylethylamine (18 mg, 0.138 mmol, 24 μL) were added to a solution of **3.184** (9 mg, 0.046 mmol) in CH_2Cl_2 (100 μL) at 0 ˚C. After 30 min, the ice bath was removed, and the reaction was stirred at rt for 24 h. Aqueous 1N HCl (0.1 mL) was added. The layers were separated, and the aqueous layers were extracted with CH_2Cl_2 (3 x 1 ml). The organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (10:1) to yield 4 mg (50%) of **3.187** as a colorless oil. ^{1}H NMR (400 MHz) δ 6.13 (dd, J = 2.7, 1.0 Hz, 1 H), 5.97 (d, J = 3.1 Hz, 1 H), 5.89 (dd, J = 3.1, 1.0 Hz, 1 H), 5.35 (dd, J = 2.4, 1.0 Hz, 1 H), 4.04–3.96 (m, 1 H), 2.54–2.06 (comp, 4 H), 2.26 (s, 3 H); ^{13}H NMR (100 MHz) δ 206.0, 153.7, 151.8, 146.1, 119.5, 106.8, 106.2, 41.0, 37.3, 26.2, 14.3.

NMR Assignments: ^{1}H NMR (400 MHz) δ 6.13 (dd, J = 2.7, 1.0 Hz, 1 H, C11-H), 5.97 (d, J = 3.1 Hz, 1 H, C3-H), 5.89 (dd, J = 3.1, 1.0 Hz, 1 H, C4-H),

5.35 (dd, J = 2.4, 1.0 Hz, 1 H, C11-H), 4.04–3.96 (m, 1 H, C6-H), 2.54–2.06 (comp, 4 H, C8-H & C7-H), 2.26 (s, 3 H, C1-H); ^{13}H NMR (100 MHz) δ 206.0 (C9), 153.7 (C10), 151.8 (C5), 146.1 (C2), 119.5 (C11), 106.8 (C3), 106.2 (C4), 41.0 (C6), 37.3 (C8), 26.2 (C7), 14.3 (C1).



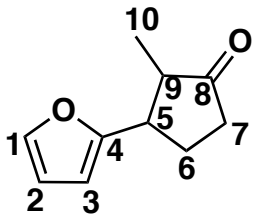
3.178

3-(Furan-2-yl)-2-methylcyclopentanone (3.178). *n*-BuLi (2.23 M in hexanes, 1.22 mmol, 0.54 mL) was added to a solution of furan (84 mg, 1.2 mmol, 90 μL) in THF (2 mL) at –78 ˚C. The resultant solution was stirred –78 ˚C for 20 min and 0 ˚C for 2 h, whereupon $Ti(OiPr)_4$ (398 mg, 1.4 mmol, 416 μL) was added at –78 ˚C. The reaction mixture was stirred for 1 h and then added via cannula to a solution of cyclopentenone (49 mg, 0.6 mmol, 50 μL), 10 mol % $[RhCl((S)\text{-binap})]_2$ (generated *in situ* from $[Rh(cod)Cl]_2$ and (*S*)-BINAP), and $ClSiEt_3$ (98 mg, 0.9 mmol, 115 μL) in THF (2 mL). The reaction mixture was stirred at room temperature for 12 h. Saturated aqueous $NaHCO_3$ (2.0 mL) was added, and the biphasic mixture was filtered through celite, eluting with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and used without further purification. Methyllithium (1.53 M in

Et_2O, 0.60 mL, 0.92 mmol) was added to a solution of the TES enol ether intermediate in PhMe (5 mL) at –78 ˚C. This solution was stirred at –78 ˚C for 20 min, and at 0 ˚C for 30 min. The reaction was warmed to 0 ˚C and stirred for 30 min. HMPA (515 mg, 0.5 mL, 2.9 mmol) was added to the solution and stirring was continued for 15 min. $ClTi(OiPr)_3$ (81 mg, 0.31 mmol, 74 μL) was then added and the resultant solution was stirred for 30 min. The mixture was cooled to –78 ˚C, MeI (264 mg, 1.86 mmol, 116 μL) was added, and the resultant mixture was stirred for 16 h at –78 ˚C. Saturated aqueous NH_4Cl (3 mL) and Et_2O (5 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 70 mg (70%) of **3.178** as a colorless oil. ^{1}H NMR (400 MHz) δ 7.35 (dd, J = 1.8, 0.8 Hz, 1 H), 6.32 (dd, J = 3.1, 1.8 Hz, 1 H), 6.10 (app dt, J = 3.1, 0.8 Hz, 1 H), 2.93 (app td, J = 11.4, 6.1 Hz, 1 H), 2.49 (dd, J = 18.6, 8.1 Hz 1 H), 2.36-2.19 (comp, 3 H), 2.07-1.96 (m, 1 H), 1.13 (d, J = 7.0 Hz); ^{13}C NMR (125 MHz) δ 219.1, 156.2, 141.5, 110.1, 104.9, 49.4, 43.8, 37.2, 26.6, 12.8; IR (neat) 2968, 2877, 1800, 1740, 1456, 1164, 1150, 1011, 739 cm^{-1}; mass spectrum (CI) m/z 165.0918 ($C_{10}H_{13}O_2$ (M+1) requires 165.0916), 111 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.35 (dd, J = 1.8, 0.8 Hz, 1 H, C1-H), 6.32 (dd, J = 3.1, 1.8 Hz, 1 H, C2-H), 6.10 (app dt, J = 3.1, 0.8 Hz, 1 H, C3-H), 2.93 (app td, J = 11.4, 6.1 Hz, 1 H, C5-H), 2.49 (dd, J = 18.6, 8.1 Hz 1 H, C7-H), 2.36-2.19 (comp, 3 H, C9-H & C6-H & C7-H), 2.07-1.96 (m, 1 H, C6-H),

1.13 (d, J = 7.0 Hz, 3 H, C10-H); ^{13}C NMR (125 MHz) δ 219.1 (C8), 156.2 (C4), 141.5 (C1), 110.1 (C2), 104.9 (C3), 49.4 (C9), 43.8 (C5), 37.2 (C7), 26.6 (C6), 12.8 (C10).



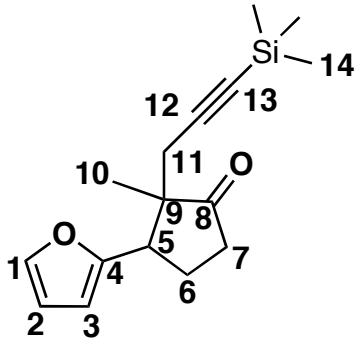
3.178

Racemic 3-(Furan-2-yl)-2-methylcyclopentanone (3.178) (AJS-V-197). This procedure was used for the preparation of racemic **3.178** on large scale. Furan-2-yl zinc chloride **2.102** was prepared according to the general procedure (vide supra). The solution of **2.102** (0.5 M in THF, 200 mL) was transferred via cannula to a solution of 2-methylcyclopent-2-enone (7.70 g, 80.0 mmol, 7.9 mL) and TMSCl (13.1 g, 120 mmol, 15.3 mL) in THF (100 mL) and stirred at room temperature for 12 h. Aqueous 1N HCl (80 mL) was added to the reaction and the resultant mixture was stirred at room temperature for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (5 x 50 mL). The organic layers were combined and washed with $NaHCO_3$ (80 mL). The organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 13.14 g (100%) of **3.178** as a colorless oil and as a mixture of cis/trans isomers (0.6:1.0): ^{1}H NMR (600 MHz) δ 7.35 (dd, J = 1.8, 0.8 Hz, 1 H, *trans*-isomer), 7.30 (dd, J =

1.8, 0.8 Hz, 0.6 H, *cis*-isomer), 6.32 (dd, *J* = 3.1, 1.8 Hz, 1 H, *trans*-isomer), 6.28 (dd, *J* = 3.2, 1.8 Hz, 0.6 H, *cis*-isomer), 6.10 (app dt, *J* = 3.1, 0.8 Hz, 1 H, *trans*-isomer), 6.04 (app dt, *J* = 3.2, 0.8 Hz, 0.6 H, *cis*-isomer), 3.61–3.59 (m, 0.6 H, *cis*-isomer), 2.93 (*app* td, *J* = 11.4, 6.1 Hz, 1 H, *trans*-isomer), 2.49 (comp, 2.2 H), 2.36-2.19 (comp, 4.8 H), 2.07-1.96 (m, 1 H), 1.13 (d, *J* = 7.0 Hz, 3 H, *trans*-isomer), 0.84 (d, *J* = 7.3 Hz, 1.8 H, *cis*-isomer); ^{13}C NMR (125 MHz) δ 219.9 (*cis*-isomer), 219.0 (*trans*-isomer), 156.2 (*trans*-isomer), 155.7 (*cis*-isomer), 141.6 (*cis*-isomer), 141.5 (*trans*-isomer), 110.1 (*trans*-isomer), 109.9 (*cis*-isomer), 106.2 (*cis*-isomer), 104.9 (*trans*-isomer), 49.4 (*trans*-isomer), 47.8 (*cis*-isomer), 43.8 (*trans*-isomer), 39.9 (*cis*-isomer), 37.2 (*trans*-isomer), 36.1 (*cis*-isomer), 26.6 (*trans*-isomer), 25.5 (*cis*-isomer), 12.8 (*trans*-isomer), 10.6 (*cis*-isomer); IR (neat) 2970, 1740, 1275, 1261, 1150, 1010, 750 cm^{-1}; mass spectrum (CI) *m/z* 165.0917 ($C_{10}H_{13}O_2$ (M+1) requires 165.0916), 165 (base).

NMR Assignments: ^{1}H NMR (600 MHz) δ 7.35 (dd, *J* = 1.8, 0.8 Hz, 1 H, *trans*-isomer, C1-H), 7.30 (dd, *J* = 1.8, 0.8 Hz, 0.6 H, *cis*-isomer, C1-H), 6.32 (dd, *J* = 3.1, 1.8 Hz, 1 H, *trans*-isomer, C2-H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 0.6 H, *cis*-isomer, C2-H), 6.10 (app dt, *J* = 3.1, 0.8 Hz, 1 H, *trans*-isomer, C3-H), 6.04 (app dt, *J* = 3.2, 0.8 Hz, 0.6 H, *cis*-isomer, C3-H), 3.61–3.59 (m, 0.6 H, *cis*-isomer, C5-H), 2.93 (*app* td, *J* = 11.4, 6.1 Hz, 1 H, *trans*-isomer, C5-H), 2.49 (comp, 2.2 H, C9-0.6H, C7-0.6H, C7-H), 2.36-2.19 (comp, 4.8 H, C7-H, C7-0.6H, C9-H, C6-H, C6-1.2H), 2.07-1.96 (m, 1 H, C6-H), 1.13 (d, *J* = 7.0 Hz, 3 H, *trans*-isomer, C10-H), 0.84 (d, *J* = 7.3 Hz, 1.8 H, *cis*-isomer, C10-1.8 H); ^{13}C NMR (125 MHz) δ 219.9 (*cis*-isomer, C8), 219.0 (*trans*-isomer, C8), 156.2 (*trans*-isomer, C4), 155.7

(*cis*-isomer, C4), 141.6 (*cis*-isomer, C1), 141.5 (*trans*-isomer, C1), 110.1 (*trans*-isomer, C2), 109.9 (*cis*-isomer, C2), 106.2 (*cis*-isomer, C3), 104.9 (*trans*-isomer, C3), 49.4 (*trans*-isomer, C9), 47.8 (*cis*-isomer, C9), 43.8 (*trans*-isomer, C5), 39.9 (*cis*-isomer, C5), 37.2 (*trans*-isomer, C7), 36.1 (*cis*-isomer, C7), 26.6 (*trans*-isomer, C6), 25.5 (*cis*-isomer, C6), 12.8 (*trans*-isomer, C10), 10.6 (*cis*-isomer, C10).

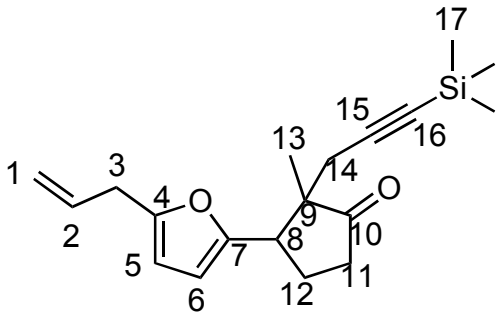


3.188

3-(Furan-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (3.188) (AJS-V-266). NaHMDS (1.9 M in THF, 3.15 mmol, 57 μL) was added to a solution of **3.178** (575 mg, 3.5 mmol) in THF (30 mL) at –78 ˚C. After stirring for 20 min, the cold bath was removed, and stirring was continued at room temperature for 1.5 h. 3-(Iodoprop-1-ynyl)trimethylsilane (86 mg, 0.36 mmol, *prepared immediately prior to use*[i]) was added at 0 ºC and the resultant solution was stirred for 2 h. Saturated aqueous NH_4Cl (1.0 mL) and Et_2O (15 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by

flash chromatography, eluting with pentane/Et_2O (4:1) to yield 778 mg (81%) of **3.188** as a colorless oil. ^{1}H NMR (400 MHz) δ 7.36 (dd, J = 1.9, 0.9 Hz, 1 H), 6.33 (ddd, J = 3.2, 1.9, 0.3 Hz, 1 H), 6.14 (dt, J = 3.2, 0.8 Hz, 1 H), 3.78 (dd, J = 11.4, 6.3, 1 H), 2.58 (d, J = 16.8 Hz, 1 H), 2.40 (d, J = 16.8 Hz, 1 H), 2.57-2.52 (m, 1 H), 2.32-2.10 (comp, 3 H), 0.70 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.4, 154.8, 141.7, 109.9, 106.5, 103.4, 87.4, 52.4, 42.3, 37.6, 27.5, 22.8, 18.3, 0.1; IR (CH_2Cl_2) 2963, 2899, 2175, 1745, 1250, 844, 760 cm^{-1}; mass spectrum (CI) m/z 275.1472 [$C_{16}H_{23}O_2Si$ (M+1) requires 275.1467], 275 (base), 259.

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.36 (dd, J = 1.9, 0.9 Hz, 1 H, C1-H), 6.33 (ddd, J = 3.2, 1.9, 0.3 Hz, 1 H, C2-H), 6.14 (dt, J = 3.2, 0.8 Hz, 1 H, C3-H), 3.78 (dd, J = 11.4, 6.3, 1 H, C5-H), 2.58 (d, J = 16.8 Hz, 1 H), 2.40 (d, J = 16.8 Hz, 1 H), 2.57-2.52 (m, 1 H, C7-H), 2.32-2.10 (comp, 3 H, C7-H & C6-H), 0.70 (s, 3 H, C10-H), 0.13 (s, 9 H, C14-H);^{13}C NMR (125 MHz) δ 219.4 (C8), 154.8 (C4), 141.7 (C1), 109.9 (C2), 106.5 (C3), 103.4 (C13), 87.4 (C12), 52.4 (C9), 42.3 (C5), 37.6 (C7), 27.5 (C11), 22.8 (C6), 18.3 (C10), 0.1 (C14).

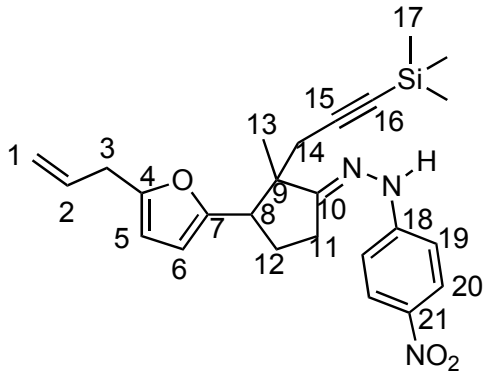


3.193

3-(5-Allylfuran-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (3.193) (AJS-V-230). NaHMDS (1.91 M in THF, 9.0 mmol, 4.7 mL) was added to a solution of **3.198** (2.04 g, 10 mmol) in THF (100 mL) at –78 ˚C. After stirring for 10 min at –78 ˚C, the cold bath was removed, and stirring was continued for 1 h. (3-iodoprop-1-ynyl)trimethylsilane (3.57 g, 15.0 mmol, *prepared immediately prior to use according to literature procedures*)[160, 161] was added at 0 ˚C and the resultant solution was stirred for 2 h. Saturated aqueous NH_4Cl (5.0 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 2.61 g (83%) of **3.193** as a single diastereomer and as a colorless oil. ^{1}H NMR (600 MHz) δ 6.03 (d, J = 3.1 Hz, 1H), 5.95 (d, J = 3.1 Hz, 1H), 5.80 (ddt, J = 16.6, 10.1, 6.5 Hz, 1 H), 5.12 (dq, J = 16.6, 1.6 Hz, 1 H), 5.10 (dq, J = 10.1, 1.4 Hz, 1 H), 3.72 (dd, J = 11.4, 6.1 Hz, 1 H), 3.36 (dd, J = 6.5, 1.1 Hz, 2 H), 2.57 (d, J = 16.9 Hz, 1 H), 2.53 (m, 1 H), 2.36 (d, J = 16.9 Hz, 1 H), 2.29–2.25 (m, 1 H), 2.25–2.19 (m, 1 H), 2.14–2.07 (m, 1 H), 0.71 (s, 3 H), 0.13

(s, 9 H); ^{13}C NMR (150 MHz) δ 219.7, 153.4, 153.0, 133.9, 116.7, 107.2, 105.9, 103.6, 87.3, 52.3, 42.4, 37.6, 32.6, 27.5, 22.8, 18.4, 0.12; IR (CH_2Cl_2) 2963, 2899, 2175, 1745, 1249, 843, 786, 759 cm^{-1}; mass spectrum (CI) *m/z* 315.1776 [$C_{19}H_{27}O_2Si$ (M+1) requires 315.1780], 315 (base), 299.

NMR Assignments: ^{1}H NMR (600 MHz) δ 6.03 (d, *J* = 3.1 Hz, 1H, C5-H), 5.95 (d, *J* = 3.1 Hz, 1H, C6-H), 5.80 (ddt, *J* = 16.6, 10.1, 6.5 Hz, 1 H, C2-H), 5.12 (dq, *J* = 16.6, 1.6 Hz, 1 H, C1-H), 5.10 (dq, *J* = 10.1, 1.4 Hz, 1 H, C1-H), 3.72 (dd, *J* = 11.4, 6.1 Hz, 1 H, C8-H), 3.36 (dd, *J* = 6.5, 1.1 Hz, 2 H, C3-H), 2.57 (d, *J* = 16.9 Hz, 1 H, C14-H), 2.53 (m, 1 H, C11-H), 2.36 (d, *J* = 16.9 Hz, 1 H, C14-H), 2.29–2.25 (m, 1 H, C12-H), 2.25–2.19 (m, 1 H, C11-H), 2.14–2.07 (m, 1 H, C12-H), 0.71 (s, 3 H, C13-Me), 0.13 (s, 9 H, TMS); ^{13}C NMR (150 MHz) δ 219.7 (C10), 153.4 (C4), 153.0 (C7), 133.9 (C2), 116.7(C1), 107.2 (C5), 105.9 (C6), 103.6 (C16), 87.3 (C15), 52.3 (C9), 42.4 (C8), 37.6 (C11), 32.6 (C3), 27.5 (C14), 22.8 (C12), 18.4 (C13), 0.12 (C17).

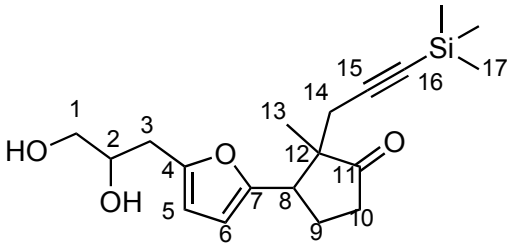


3.199

(*E*)-1-(3-(5-Allylfuran-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentylidene)-2-(4-nitrophenyl)hydrazine (3.199) (AJS-V-225). Para-nitrophenylhydrazine (9.2 mg, 0.06 mmol) was added to a solution of **3.193** (19 mg, 0.06 mmol) in acetic acid (0.6 mL) and stirred at rt for 20 min and then at 80 ˚C for 2 h. The reaction mixture was poured onto wet ice; extracted with EtOAc (3 x 3 ml); washed with saturated aqueous $NaHCO_3$; dried ($MgSO_4$); and concentrated. 17.5 mg (65%) of **3.199** was isolated. ^{1}H NMR (600 MHz) δ 8.15 (d, J = 9.3 Hz, 2H), 7.29 (s, 1 H), 7.07 (d, J = 9.3 Hz, 2H), 6.02 (d, J = 3.1 Hz, 1 H), 5.95 (d, J = 3.1 Hz, 1 H), 5.92 (ddt, J = 16.7, 10.1, 6.5 Hz, 1 H), 5.13 (dq, J = 16.7, 1.6 Hz, 1 H), 5.10 (dq, J = 10.1, 1.6 Hz, 1 H), 3.50 (dd, J = 11.2, 6.5 Hz, 1 H), 3.36 (dd, J = 6.5, 1.1 Hz, 2 H), 2.73 (d, J = 16.7 Hz, 1 H), 2.66–2.61 (m, 1 H), 2.52 (d, J = 16.7 Hz, 1 H), 2.33–2.13 (comp, 3 H), 0.89 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR (150 MHz) δ 161.3, 153.1, 152.9, 150.4, 140.0, 134.0, 126.1, 116.7, 111.8, 107.4, 105.9, 105.0, 88.7, 49.5, 44.5, 32.6, 29.8, 25.8, 25.1, 21.6, 0.2.

NMR Assignments: ^{1}H NMR (600 MHz) δ 8.15 (d, J = 9.3 Hz, 2H, C20-H), 7.29 (s, 1 H, N-H), 7.07 (d, J = 9.3 Hz, 2H, C19-H), 6.02 (d, J = 3.1 Hz,

1 H, C5-H), 5.95 (d, *J* = 3.1 Hz, 1 H, C6-H), 5.92 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1 H, C2-H), 5.13 (dq, *J* = 16.7, 1.6 Hz, 1 H, C1-H), 5.10 (dq, *J* = 10.1, 1.6 Hz, 1 H, C1-H), 3.50 (dd, *J* = 11.2, 6.5 Hz, 1 H, C8-H), 3.36 (dd, *J* = 6.5, 1.1 Hz, 2H, C3-H), 2.73 (d, *J* = 16.7 Hz, 1 H, C14-H), 2.66–2.61 (m, 1 H, C11-H), 2.52 (d, *J* = 16.7 Hz, 1 H, C14-H), 2.33–2.13 (comp, 3 H, C11-H & C12-H), 0.89 (s, 3 H, C13-Me), 0.09 (s, 9 H, C17-H); ^{13}C NMR (150 MHz) δ 161.3 (C10), 153.1 (C18), 152.9 (C4), 150.4 (C7), 140.0 (C21), 134.0 (C2), 126.1 (C20), 116.7 (C1), 111.8 (C19), 107.4 (C5), 105.9 (C6), 105.0 (C15), 88.7 (C16), 49.5 (C9), 44.5 (C8), 32.6 (C3), 29.8 (C14), 25.8 (C11), 25.1 (C12), 21.6 (C13), 0.2 (C17).



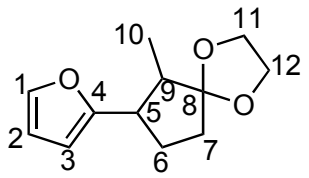
3.200

3-(5-(2,3-dihydroxypropyl)furan-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (3.200) (AJS-V-248). Furan **3.193** (587 mg, 1.83 mmol) was added to a solution of ADMix-β (2.6 g) and methanesulfonamide (348 mg, 3.66 mmol) in tBuOH/H_2O (9 mL:9 mL) at room temperature. The resultant mixture was stirred at room temperature for 4 d. Saturated aqueous sodium metabisulfite (10.0 mL) and EtOAc (10.0 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL), and the combined organic layers were dried ($MgSO_4$) and

concentrated under reduced pressure. The excess methanesulfonamide was removed via precipitation with CH_2Cl_2. The residue was purified by flash chromatography, eluting with pentane/EtOAc (4:1→1:1) to yield 319 mg (50%) of **3.200** as a colorless oil: ^{1}H NMR (500 MHz) δ 6.08–6.06 (comp, 2 H), 4.00–3.98 (m, 1 H), 3.75–3.69 (comp, 2 H), 3.53 (ddd, *J* = 11.2, 6.3, 1.5 Hz, 1 H), 2.82 (d, *J* = 6.6 Hz, 2 H), 2.62 (d, *J* = 16.8 Hz, 0.5 H), 2.60 (d, *J* = 16.8 Hz, 0.5 H), 2.56–2.52 (comp, 2 H), 2.37 (d, *J* = 16.8 Hz, 0.5 H), 2.36 (d, *J* = 16.8 Hz, 0.5 H), 2.29–2.08 (comp, 4 H), 1.95–1.90 (br s, 1 H), 0.71 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.3, 153.84, 153.82, 150.9, 150.8, 107.7, 107.6, 107.3, 107.2, 103.2, 87.4, 70.6, 70.5, 65.9, 52.2, 43.4, 42.2, 42.1, 37.4, 32.3, 27.3, 22.6, 22.5, 18.3, 0.1; IR (CH_2Cl_2) 3399, 2961, 2898, 1742, 1329, 1249, 1074, 1032, 844, 760 cm^{-1}; mass spectrum (CI) *m/z* 349.1837 [$C_{19}H_{29}O_4Si$ (M+1) requires 349.1835], 377, 349 (base), 333.

NMR Assignments: ^{1}H NMR (500 MHz) δ 6.08–6.06 (comp, 2 H, C5-H & C6-H), 4.00–3.98 (m, 1 H, C2-H), 3.75–3.69 (comp, 2 H, C1-H & C8-H), 3.53 (ddd, *J* = 11.2, 6.3, 1.5 Hz, 1 H, C1-H), 2.82 (d, *J* = 6.6 Hz, 2 H, C3-H), 2.62 (d, *J* = 16.8 Hz, 0.5 H, C14-H), 2.60 (d, *J* = 16.8 Hz, 0.5 H, C14-H), 2.56–2.52 (m, 1 H, C10-H), 2.37 (d, *J* = 16.8 Hz, 0.5 H, C14-H), 2.36 (d, *J* = 16.8 Hz, 0.5 H, C14-H), 2.29–2.08 (comp, 4 H, C10-H, C9-H, & OH), 1.95–1.90 (br s, 1 H, OH), 0.71 (s, 3 H, C13-H), 0.13 (s, 9 H, C17-H); ^{13}C NMR (125 MHz) δ 219.3 (C11), 153.84 (C4), 153.82 (C4), 150.9 (C7), 150.8 (C7), 107.7 (C5), 107.6 (C5), 107.3 (C6), 107.2 (C6), 103.2 (C16), 87.4 (C15), 70.6 (C2), 70.5 (C2), 65.9 (C1), 52.2

(C12), 42.2 (C8), 42.1 (C8), 37.4 (C10), 32.3 (C3), 27.3 (C14), 22.6 (C9), 22.5 (C9), 18.3 (C13), 0.1 (C17).

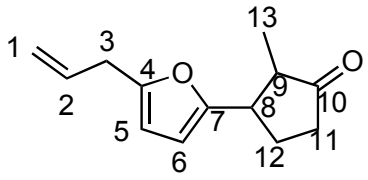


3.196

7-(furan-2-yl)-6-methyl-1,4-dioxaspiro[4.4]nonane (3.196) (AJS-V-24). Pyridinium para-toluenesulfonate (56 mg, 0.24 mmol) and ethylene glycol (379 mg, 341 μL) were added to a solution of **3.178** (200 mg, 1.22 mmol) in benzene (12.0 mL). The solution was heated under reflux with a Dean-Stark apparatus for 4 h. Saturated aqueous $NaHCO_3$ (2.0 mL) was added, followed by CH_2Cl_2 (5.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with pentane/Et_2O (10:1) to yield 254 mg (100%) of **3.196** as a colorless oil: ^{1}H NMR (500 MHz) δ 7.32 (dd, J = 1.8, 0.7 Hz, 0.2 H), 7.31 (dd, J = 1.8, 0.9 Hz, 0.8 H), 6.29 (ddd, J = 3.2, 1.9, 0.4 Hz, 0.2 H), 6.28 (ddd, J = 3.2, 1.9, 0.4 Hz, 0.8 H), 6.04 (dt, J = 3.2, 0.9 Hz, 0.2 H), 6.02 (dt, J = 3.2, 0.8 Hz, 0.8 H), 3.98–3.86 (comp, 4 H), 3.47 (dd, J = 17.6, 7.7 Hz, 0.2 H), 2.81 (dt, J = 11.2, 8.9 Hz, 0.8 H), 2.29–2.24 (m, 0.2 H), 2.19–2.15 (m, 0.8 H), 2.10–1.94 (comp, 2 H), 1.93–1.79 (comp, 2 H), 0.96 (d, J = 6.8 Hz, 2.4 H), 0.68 (d, J = 7.3 Hz, 0.6 H); ^{13}C NMR (125 MHz) δ 157.9, 157.0, 141.1, 141.0, 118.7, 117.4, 109.9, 109.8, 105.7, 104.3, 64.9, 64.88, 64.82, 64.0, 46.7, 43.8, 43.7, 40.0, 35.4, 33.2, 27.5, 24.3, 11.6,

10.4; IR (CH_2Cl_2) 2969, 2878, 1507, 1149, 1110, 1034, 948, 912, 731 cm^{-1}; mass spectrum (CI) *m/z* 209.1176 [$C_{12}H_{17}O_3$ (M+1) requires 209.1178], 209, 197 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.32 (dd, *J* = 1.8, 0.7 Hz, 0.2 H, C1-H), 7.31 (dd, *J* = 1.8, 0.9 Hz, 0.8 H, C1-H), 6.29 (ddd, *J* = 3.2, 1.9, 0.4 Hz, 0.2 H, C2-H), 6.28 (ddd, *J* = 3.2, 1.9, 0.4 Hz, 0.8 H, C2-H), 6.04 (dt, *J* = 3.2, 0.9 Hz, 0.2 H, C3-H), 6.02 (dt, *J* = 3.2, 0.8 Hz, 0.8 H, C3-H), 3.98–3.86 (comp, 4 H, C11-H & C12-H), 3.47 (dd, *J* = 17.6, 7.7 Hz, 0.2 H, C5-H), 2.81 (dt, *J* = 11.2, 8.9 Hz, 0.8 H, C5-H), 2.29–2.24 (m, 0.2 H, C9-H), 2.19–2.15 (m, 0.8 H, C9-H), 2.10–1.94 (comp, 2 H, C7-H), 1.93–1.79 (comp, 2 H, C6-H), 0.96 (d, *J* = 6.8 Hz, 2.4 H, C10-Me), 0.68 (d, *J* = 7.3 Hz, 0.6 H, C10-Me); ^{13}C NMR (125 MHz) δ 157.9 (C4-major), 157.0 (C4-minor), 141.1 (C1-major), 141.0 (C1-minor), 118.7 (C8-minor), 117.4 (C8-major), 109.9 (C2-major), 109.8 (C2-minor), 105.7 (C3-minor), 104.3 (C3-major), 64.9 (C11-minor), 64.88 (C11-major), 64.82 (C12-major), 64.0 (C12-minor), 46.7 (C9-major), 43.8 (C9-minor), 43.7 (C5-major), 40.0 (C5-minor), 35.4 (C7-major), 33.2 (C7-minor), 27.5 (C6-major), 24.3 (C6-minor), 11.6 (C10-major), 10.4 (C10-minor).

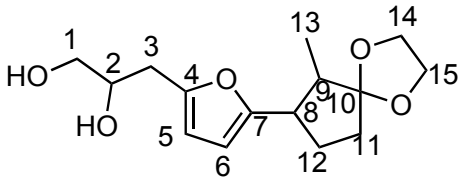


3.198

3-(5-allylfuran-2-yl)-2-methylcyclopentanone (3.198). (AJS-V-228). Pyridinium *p*-toluenesulfonate (3.58g, 15.6 mmol) was added to a solution of **3.197** (6.46g, 26 mmol) in 260 mL of acetone:H_2O (14:1). The resultant solution was heated under reflux for 4 h. Saturated aqueous $NaHCO_3$ (20.0 mL) and Et_2O (25.0 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (5 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (10:1) to yield 5.31 g (100%) of **3.198** as a colorless oil: ^{1}H NMR (500 MHz) δ 6.00 (d, J = 3.1 Hz, 1 H), 5.98–5.89 (comp, 2 H), 5.16–5.09 (comp, 2 H), 3.37 (dd, J = 6.5, 1.2 Hz, 2 H), 2.88 (td, J = 11.4, 6.0 Hz, 1 H), 2.47 (dd, J = 18.1, 8.7 Hz, 1 H), 2.34–2.19 (comp, 3 H), 2.04–1.95 (m, 1 H), 1.13 (d, J = 7.0, 3 H); ^{13}C NMR (125 MHz) δ 219.3, 154.9, 152.9, 133.9, 116.8, 105.9, 105.5, 49.4, 43.9, 37.2, 32.6, 26.7, 12.8; IR ($CHCl_2$) 2967, 2932, 2878, 1742, 1564, 1456, 1161, 1015, 919, 786 cm^{-1}; mass spectrum (CI) m/z 205.1223 [$C_{13}H_{17}O_2$ (M+1) requires 205.1229], 205 (base).

NMR ASSIGNMENTS: ^{1}H NMR (500 MHz) δ 6.00 (d, J = 3.1 Hz, 1 H, C6-H), 5.98–5.89 (comp, 2 H, C5-H & C2-H), 5.16–5.09 (comp, 2 H, C1-H), 3.37 (dd, J = 6.5, 1.2 Hz, 2 H, C3-H), 2.88 (td, J = 11.4, 6.0 Hz, 1 H, C8-H), 2.47 (dd, J = 18.1, 8.7 Hz, 1 H, C11-H), 2.34–2.19 (comp, 3 H, C11-H, C12-H, & C9-H),

2.04–1.95 (m, 1 H, C12-H), 1.13 (d, J = 7.0, 3 H, C13-Me); ^{13}C NMR (125 MHz) δ 219.3 (C10), 154.9 (C4), 152.9 (C7), 133.9 (C2), 116.8 (C1), 105.9 (C5), 105.5 (C6), 49.4 (C9), 43.9 (C8), 37.2 (C11), 32.6 (C3), 26.7 (C12), 12.8 (C13).

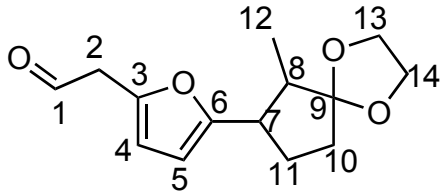


3.204

3-(5-(6-Methyl-1,4-dioxaspiro[4.4]nonan-7-yl)furan-2-yl)propane-1,2-diol (3.204). Furan **3.203** (250 mg, 1.01 mmol) was added to a solution of ADMix-α and methanesulfonamide (192 mg, 2.02 mmol) in *t*BuOH-H_2O (5 mL:5 mL) at rt. The resultant mixture was stirred for 2.5 d. Two major diastereomers were isolated. Saturated aqueous sodium metabisulfite (5 mL) was added, followed by EtOAc (5.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The excess methanesulfonamide was removed via precipitation with CH_2Cl_2. The residue was purified by flash chromatography, eluting with pentane/EtOAc (4:1→1:1) to yield 141 mg (50%) of **3.204** as a colorless oil. ^{1}H NMR (500 MHz) δ 6.02 (d, J = 2.9 Hz, 1 H), 5.94 (d, J = 3.2 Hz, 1 H), 4.07–3.87 (comp, 5 H), 3.72–3.68 (m, 1 H), 3.55–3.51 (m, 1 H), 2.80 (d, J = 4.1 Hz, 2 H), 2.78–2.74 (m, 1 H), 2.21 (d, J = 4.1 Hz, 1 H), 2.13 (ddd, J = 13.4, 11.2, 6.6 Hz, 1 H), 2.05–1.9 (comp, 3 H), 1.87–1.77 (comp, 2 H), 0.95 (d, J = 6.8 Hz, 2.6 H, methyl), 0.67 (dd, J = 7.1, 3.2 Hz, 0.4 H,

methyl); ^{13}C NMR (125 MHz) δ 157.3, 150.1, 117.4, 107.72, 107.70, 105.1, 70.8, 70.7, 66.0, 64.9, 64.8, 46.7, 46.6, 43.7, 43.5, 35.4, 32.4, 27.5, 27.4, 11.7; IR (CH_2Cl_2) 3368, 2964, 2879, 1457, 1328, 1155, 1107, 1032, 913, 787 cm^{-1}; mass spectrum (CI) *m/z* 283.1544 [$C_{15}H_{23}O_5$ (M+1) requires 283.1545], 283, 265 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 6.02 (d, *J* = 2.9 Hz, 1 H, C5-H), 5.94 (d, *J* = 3.2 Hz, 1 H, C6-H), 4.07–3.87 (comp, 5 H, C15-H, C14-H, & C2-H), 3.72–3.68 (m, 1 H, C1-H), 3.55–3.51 (m, 1 H, C1-H), 2.80 (d, *J* = 4.1 Hz, 2 H, C3-H), 2.78–2.74 (m, 1 H, C8-H), 2.21 (d, *J* = 4.1 Hz, 1 H, C12-H), 2.13 (ddd, *J* = 13.4, 11.2, 6.6 Hz, 1 H, C9-H), 2.05–1.9 (comp, 3 H, C11-H & OH), 1.87–1.77 (comp, 2 H, C12-H & OH), 0.95 (d, *J* = 6.8 Hz, 3 H, methyl); ^{13}C NMR (125 MHz) δ 157.3 (C4), 150.1 (C7), 117.4 (C10), 107.72 (C5), 107.70 (C5), 105.1 (C6), 70.8 (C2), 70.7 (C2), 66.0 (C1), 64.9 (C14), 64.8 (C15), 46.7 (C9), 46.6 (C9), 43.7 (C8), 35.4 (C11), 32.4 (C3), 27.5 (C12), 27.4 (C12),11.7 (C13).



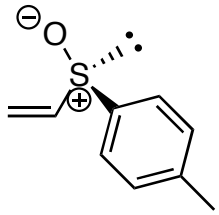
3.205

2-(5-(2-Methyl-3-oxocyclopentyl)furan-2-yl)acetaldehyde (3.205). Sodium periodate (188 mg, 0.88 mmol) was added to a solution of diol **3.204** (125 mg, 0.44 mmol) in THF/H_2O (2.2mL:2.2mL) at 0 ºC. The reaction was complete

within 45 min at 0 ºC. The THF/H_2O layers were extracted with Et_2O (3 x 5 mL), washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 110 mg (100%) of **3.205** as a colorless oil, which was carried on without further purification. A 0.45:0.55 mixture of cis/trans isomers was isolated. ^{1}H NMR (600 MHz, CH_2Cl_2) δ 9.69 (t, J = 2.1 Hz, 0.45 H), 9.68 (t, J = 2.2 Hz, 0.55 H), 6.19 (dt, J = 3.2, 0.8 Hz, 0.45 H), 6.14 (dt, J = 3.2, 0.8 Hz, 0.55 H), 6.10 (dd, J = 3.2, 0.4 Hz, 0.45 H), 6.01 (dd, J = 3.1, 0.3 Hz, 0.55 H), 3.95–3.84 (comp, 4 H), 3.68 (d, J = 1.9, 0.9 Hz, 0.9 H), 3.66 (d, J = 2.2 Hz, 1.1 H), 2.91 (td, J = 11.4, 5.9 Hz, 0.55 H), 2.78–2.73 (m, 0.45 H), 2.44 (ddt, J = 18.2, 8.1, 1.5 Hz, 0.55 H), 2.33–2.18 (comp, 2 H), 2.09 (dq, J = 11.5, 7.1 Hz, 0.55 H), 2.02–1.74 (comp, 1.9 H), 1.10 (d, J = 6.9 Hz, 1.35 H), 0.91 (d, J = 6.8 Hz, 1.65 H); ^{13}C NMR (125 MHz) δ 218.8, 197.5, 197.3, 158.8, 157.1, 145.9, 145.3, 117.6, 109.6, 109.4, 106.3, 105.8, 65.3, 65.2, 64.1, 49.7, 47.1, 44.2, 44.1, 43.7, 43.4, 43.3, 37.5, 35.7, 27.8, 26.9, 12.9, 11.8; IR (CH_2Cl_2) 2963, 2928, 1731, 1328, 1157, 1110, 1029, 789 cm^{-1}; mass spectrum (CI) m/z 251.1282 [$C_{14}H_{19}O_4$ (M+1) requires 251.1283], 253 (base), 251.

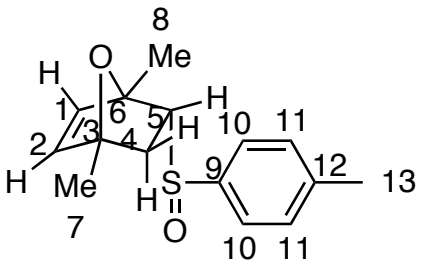
NMR ASSIGNMENTS: ^{1}H NMR (600 MHz, CH_2Cl_2) δ 9.69 (t, J = 2.1 Hz, 0.45 H, C1-H), 9.68 (t, J = 2.2 Hz, 0.55 H, C1-H), 6.19 (dt, J = 3.2, 0.8 Hz, 0.45 H, C4-H), 6.14 (dt, J = 3.2, 0.8 Hz, 0.55 H, C4-H), 6.10 (dd, J = 3.2, 0.4 Hz, 0.45 H, C5-H), 6.01 (dd, J = 3.1, 0.3 Hz, 0.55 H, C5-H), 3.95–3.84 (comp, 4 H, C13-H & C14-H), 3.68 (d, J = 1.9, 0.9 Hz, 0.9 H, C2-H), 3.66 (d, J = 2.2 Hz, 1.1 H, C2-H), 2.91 (td, J = 11.4, 5.9 Hz, 0.55 H, C7-H), 2.78–2.73 (m, 0.45 H, C7-H), 2.44 (ddt, J = 18.2, 8.1, 1.5 Hz, 0.55 H, C11-H), 2.33–2.18 (comp, 2 H, C10-H),

2.09 (dq, J = 11.5, 7.1 Hz, 0.55 H, C8-H), 2.02–1.74 (comp, 1.9 H, C8-H & C11-H), 1.10 (d, J = 6.9 Hz, 1.35 H, C12), 0.91 (d, J = 6.8 Hz, 1.65 H); ^{13}C NMR (125 MHz) δ 218.8 (C1), 158.8 (C9-major), 157.1 (C9-minor), 145.9 (C6-major), 145.3 (C6-minor), 117.6 (C3), 109.6 (C4-major), 109.4 (C4-minor), 106.3 (C5-major), 105.8 (C5-minor), 65.3 (C13), 65.2 (C14), 49.7 (C8-major), 47.1 (C8-minor), 44.2 (C7-major), 44.1 (C7-minor), 43.4 (C2-major), 43.3 (C2-minor), 37.5 (C10-major) , 35.7 (C10-minor), 27.8 (C11-major), 26.9 (C11-minor), 12.9 (C12-major), 11.8 (C12-minor).



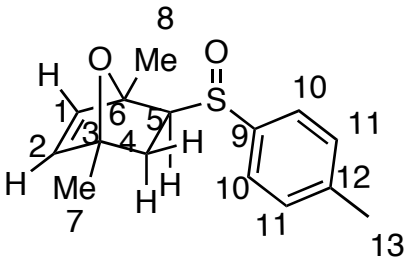
3.212

***p*-Tolylvinyl sulfoxide (3.212). (AJS-III-195).** Vinyl Grignard (0.7 M in THF, 5.1 mmol, 7.3 mL, prepared fresh from vinyl bromide and magnesium turnings) was added dropwise over 20 min to a solution of (–)-menthyl-*p*-tolylsulfinate (1.16 g, 3.9 mmol) in benzene (20 mL) at room temperature. The reaction was stirred at room temperature for 30 min. Saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The reside was purified by flash chromatography, eluting with Et_2O/EtOAc (4:1) to yield 414 mg (64%) of **3.212**. The spectroscopic data matched that in the literature.[7]



3.214-endo

+



3.214-exo

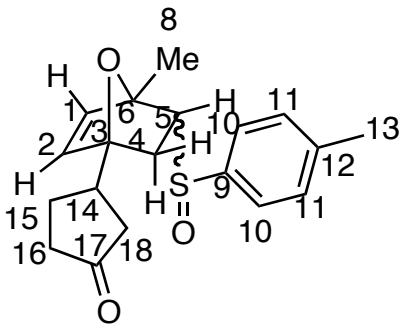
5-(*p*-Tolylsulfinyl)-1,4-dimethyl-7-oxa-bicyclo[2.2.1]hept-2-ene (*endo-exo*-3.214). (AJS-III-203). 2,5-Dimethylfuran (53 mg, 0.55 mmol, 59μL) was added to a solution of **3.212** (30 mg, 0.11 mmol) in CH_2Cl_2 (100 μL) at –20 ˚C. The reaction mixture was stirred at –20 ˚C for 36 h. Aqueous NaOH (0.2 M, 0.5 mL) was then added, and the cold bath was removed. The reaction mixture was stirred at room temperature for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 29 mg (73%) of an endo/exo mixture of **3.214** (endo/exo = 2:1, endo d.e. = 77%, exo d.e. = 82%, established by ^{1}H NMR): ^{1}H NMR for **3.214-endo** (400 MHz) δ 7.62 (d, J = 8.2 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 6.53 (d, J = 5.5 Hz, 1 H), 6.36 (d, J = 5.5 Hz, 1 H), 3.20 (dd, J = 8.9, 3.8 Hz, 0.9 H), 3.05 (d, J = 8.6, 4.1 Hz, 0.1 H), 2.40 (s, 3 H), 1.96 (s, 3 H), 1.84 (s, 3 H), 1.64 (dd, J = 12.3, 8.9 Hz, 1 H), 1.17 (dd, J = 12.3, 3.8 Hz, 1 H); MS (CI) m/z 263.1109 [$C_{15}H_{19}O_2S$ (M+1) requires 263.1106], 263 (base), 267.

^{1}H NMR for **3.214-exo** (500 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H), 7.27 (d, J = 7.8 Hz, 2H), 6.19 (d, J = 5.5 Hz, 1H), 6.13 (d, J = 5.5 Hz, 1H), 2.88 (dd, J =

8.0, 4.6 Hz, 1H), 2.38 (s, 3H), 1.93 (s, 3H), 1.52 (s, 3H), 1.27 (dd, *J* = 12.5, 8.0 Hz, 1H), 1.07 (dd, *J* = 12.5, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.40, 140.83, 140.48, 139.25, 130.09, 126.14, 87.92, 85.46, 70.91, 37.76, 21.68, 18.65, 17.62; HRMS (CI) *m/z* 263.1110 [$C_{15}H_{19}O_2S$ (M+1) requires 263.1106], 263 (base).

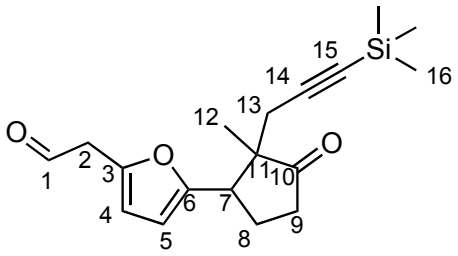
NMR Assignments FOR 3.214-endo: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.47 (m, 2H, C10-H), 7.26 (dd, *J* = 8.5, 0.6 Hz, 2H, C11-H), 6.50 (d, *J* = 5.6 Hz, 1H, C2-H), 6.33 (d, *J* = 5.6 Hz, 1H, C1-H), 3.19 (dd, *J* = 8.8, 3.9 Hz, 1H, C4-H), 2.38 (s, 3H, C13-H), 1.81 (s, 3H, C7-H), 1.61 (dd, *J* = 12.2 9.0 Hz, 1H, C5-H), 1.51 (s, 3H, C8-H), 1.15 (dd, *J* = 12.3, 3.9 Hz, 1H, C5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.25 (C9), 140.88(C12), 140.74(C1), 136.82(C2), 130.2(C11), 125.3(C10), 88.6(C3), 85.6(C6), 71.3(C4), 36.2(C5), 21.6(C13), 19.9(C7), 18.8(C8).

NMR ASSIGNMENTS FOR 3.214-exo: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 2H, C10-H), 7.27 (d, *J* = 7.8 Hz, 2H, C11-H), 6.19 (d, *J* = 5.5 Hz, 1H, C1-H), 6.13 (d, *J* = 5.5 Hz, 1H, C2-H), 2.88 (dd, *J* = 8.0, 4.6 Hz, 1H, C4-H), 2.38 (s, 3H, C13-H), 1.93 (s, 3H, C8-H), 1.52 (s, 3H, C7-H), 1.27 (dd, *J* = 12.5, 8.0 Hz, 1H, C5-H), 1.07 (dd, *J* = 12.5, 4.6 Hz, 1H, C5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4 (C9), 140.8 (C12), 140.5 (C2), 139.3 (C1), 130.1 (C11), 126.1 (C10), 87.9 (C6), 85.5 (C3), 70.9 (C4), 37.8 (C5), 21.7 (C13), 18.7 (C7), 17.6 (C8).



3.215

3-(5-(*p*-tolylsulfinyl)-4-methyl-7-oxa-bicyclo[2.2.1]hept-2-en-1-yl)cyclopentanone (3.xx) (AJS-III-219). Furan **2.100** (40 mg, 0.24 mmol) was added to a solution of **3.212** (17 mg, 0.6 mmol) in CH_2Cl_2 (200 μL) at –20 ˚C. The reaction mixture was stirred at –20 ˚C for 36 h. Aqueous NaOH (0.2 M, 0.5 mL) was added, and the reaction mixture was warmed to room temperature and stirred for an additional 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Et_2O/EtOAc (4:1) to yield 10 mg (50%) of **3.215** as a colorless oil: ^{1}H NMR for **3.215** (400 MHz) δ 7.61 (d, J = 7.9 Hz, 2 H), 7.35 (d, J = 7.9 Hz, 2 H), 6.63 (dd, J = 5.5, 2.4 Hz, 1 H), 6.50 (d, J = 5.6 Hz, 1 H), 6.49 (d, J = 5.6 Hz, 1 H), 3.30 (s, 3 H), 3.15 (dd, J = 8.8, 3.9 Hz, 1 H), 2.65-2.59 (m, 1 H), 2.36 (s, 3 H), 2.68-1.93 (comp, 6 H), 1.81-1.61 (comp, 2 H), 1.66 (s, 3 H), 1.13 (ddd, J = 16.3, 12.3, 3.9 Hz, 1 H); ^{13}C NMR (125MHz) δ 217.6, 217.5, 141.5, 140.7, 138.5, 138.4, 136.4, 136.1, 129.9, 125.1, 90.4, 90.2, 87.5, 87.4, 69.7, 69.6, 37.9, 37.8, 37.7, 31.9, 31.4, 30.4, 24.4, 24.3, 20.9, 10.4.

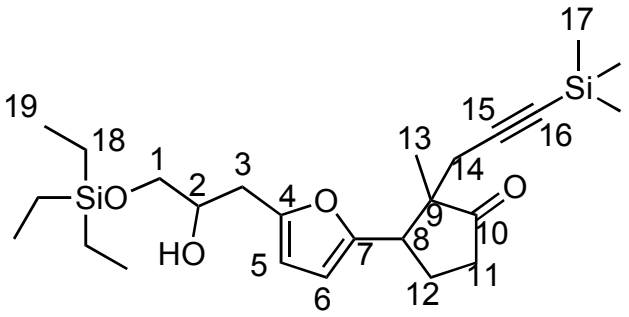


3.20

2-(5-(2-methyl-3-oxo-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentyl)furan-2-yl)acetaldehyde (3.20) (AJS-V-232). Sodium periodate (1.01 g, 4.7 mmol) was added to a solution of diol **3.200** (818 mg, 2.35 mmol) in THF/H_2O (12mL:12mL) at 0 ºC. The reaction was complete within 45 min at 0 ºC. The THF/H_2O layers were extracted with EtOAc (3 x 15 mL), washed with brine and dried (MgSO4). The solvent was removed under reduced pressure to yield 744 mg (100%) of **3.20** as a colorless oil, which was used without further purification. ^{1}H NMR (500 MHz) δ 9.71 (t, J = 2.0 Hz, 1 H), 6.19 (d, J = 3.2 Hz, 1 H), 6.13 (dd, J = 3.2, 0.7 Hz, 1 H), 3.76–3.73 (m, 1 H), 3.70 (d, J = 2.0 Hz, 2 H), 2.58 (d, J = 16.8 Hz, 1 H), 2.56–2.51 (m, 1 H), 2.35 (d, J = 16.8 Hz, 1 H), 2.31–2.09 (comp, 4 H), 0.72 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.2, 196.6, 155.1, 145.4, 109.3, 107.8, 103.4, 87.5, 52.4, 42.9, 42.3, 37.6, 27.5, 22.7, 18.4, 0.1; IR (CH_2Cl_2) 2962, 2175, 1741, 1249, 1028, 843, 760 cm^{-1}; mass spectrum (CI) m/z 317.1571 [$C_{18}H_{25}O_3Si$ (M+1) requires 317.1573], 317 (base), 301.

NMR Assignments: ^{1}H NMR (500 MHz) δ 9.71 (t, J = 2.0 Hz, 1 H, C1-H), 6.19 (d, J = 3.2 Hz, 1 H, C4-H), 6.13 (dd, J = 3.2, 0.7 Hz, 1 H, C5-H), 3.76–3.73 (m, 1 H, C7-H), 3.70 (d, J = 2.0 Hz, 2 H, C2-H), 2.58 (d, J = 16.8 Hz, 1 H,

C13-H), 2.56–2.51 (m, 1 H, C9-H), 2.35 (d, J = 16.8 Hz, 1 H, C13-H), 2.31–2.09 (comp, 3 H, C9-H & C8-H), 0.72 (s, 3 H, C12-H), 0.13 (s, 9 H, C16-H); ^{13}C NMR (125 MHz) δ 219.2 (C10), 196.6 (C1), 155.1 (C3), 145.4 (C6), 109.3 (C4), 107.8 (C5), 103.4 (C15), 87.5 (C14), 52.4 (C11), 42.9 (C7), 42.3 (C2), 37.6 (C9), 27.5 (C13), 22.7 (C8), 18.4 (C12), 0.1 (C16).

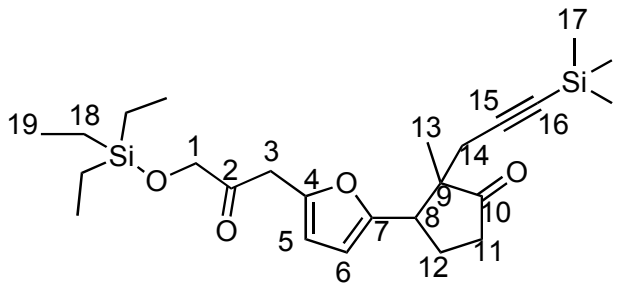


3.228

3-(5-(2-Hydroxy-3-(triethylsilyloxy)propyl)furan-2-yl)-2-methyl-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (3.228) (AJS-V-249). Chlorotriethylsilane (57 mg, 0.38 mmol, 64 μL) was added dropwise to a solution of **3.200** (120 mg, 0.34 mmol) and triethylamine (41 mg, 0.40 mmol, 56 μL) in CH_2Cl_2 (3 mL) at –15 ˚C. The reaction mixture was stirred at –15 ˚C for 1 h. Saturated aqueous $NaHCO_3$ (1.0 mL); the layers were separated; and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 134 mg (85%) of **3.228** as a colorless oil and as a 1:1 mixture of diastereomers: ^{1}H NMR (600 MHz) δ 6.04 (s, 2 H), 3.93 (m, 1 H), 3.73 (dd, J = 11.5, 6.2 Hz, 1 H), 3.64 (dd, J = 9.9, 3.8 Hz, 1 H), 3.48 (dd, J = 9.9, 6.7 Hz, 0.5 H), 3.49 (dd, J = 10.1, 6.9 Hz,

0.5 H), 2.82–2.75 (m, 2 H), 2.59 (d, J = 16.8 Hz, 0.5 H), 2.58 (d, J = 16.8 Hz, 0.5 H), 2.49 (d, J = 4.1 Hz, 0.5 H), 2.48 (d, J = 4.1 Hz, 0.5 H), 2.37 (d, J = 16.8, 1 H), 2.29–2.19 (comp, 2 H), 2.14–2.07 (m, 1 H), 0.96 (t, J = 8.1 Hz, 9 H), 0.71 (s, 3 H), 0.61 (q, J = 7.2 Hz, 6H), 0.13 (s, 9 H); ^{13}C NMR (150 MHz) δ 219.5, 153.5, 151.6, 107.4, 107.3, 107.2, 103.5, 103.4, 87.4, 87.3, 70.6, 70.5, 66.04, 66.03, 52.34, 52.33, 42.30, 42.29, 37.7, 32.1, 27.5, 22.7, 22.3, 18.4, 6.7, 4.4, 0.1; IR (CH_2Cl_2) 3480, 2956, 2913, 2876, 2175, 1744, 1249, 1112, 843 cm^{-1}; mass spectrum (CI) m/z 463.2704 [$C_{25}H_{43}O_4Si_2$ (M+1) requires 463.2700], 464, 463 (base), 445, 433.

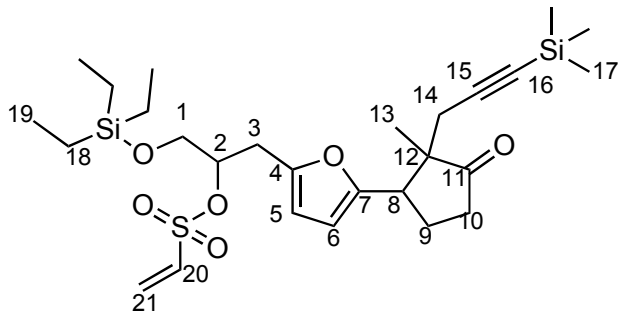
NMR ASSIGNMENTS: ^{1}H NMR (600 MHz) δ 6.04 (s, 2 H, C5-H & C6-H), 3.93 (m, 1 H, C2-H), 3.73 (dd, J = 11.5, 6.2 Hz, 1 H, C8-H), 3.64 (dd, J = 9.9, 3.8 Hz, 1 H, C1-H), 3.48 (dd, J = 9.9, 6.7 Hz, 0.5 H, C1-H), 3.49 (dd, J = 10.1, 6.9 Hz, 0.5 H, C1-H), 2.82–2.75 (m, 2 H, C3-H), 2.59 (d, J = 16.8 Hz, 0.5 H, C14-H), 2.58 (d, J = 16.8 Hz, 0.5 H, C14-H), 2.55–2.51 (m, 1H, C12-H), 2.49 (d, J = 4.1 Hz, 0.5 H, OH), 2.48 (d, J = 4.1 Hz, 0.5 H, OH), 2.37 (d, J = 16.8, 1 H, C14-H), 2.29–2.19 (comp, 2 H, C11-H & C12-H), 2.14–2.07 (m, 1 H, C12-H), 0.96 (t, J = 8.1 Hz, 9 H), 0.71 (s, 3 H), 0.61 (q, J = 7.2 Hz, 6H), 0.13 (s, 9 H); ^{13}C NMR (150 MHz) δ 219.5 (C10), 153.5 (C4), 151.6 (C7), 107.4 (C6), 107.3 (C5), 107.2 (C5), 103.5 (C16), 103.4 (C16), 87.4 (C16), 87.3 (C16), 70.6 (C2), 70.5 (C2), 66.04 (C1), 66.03 (C1), 52.34 (C9), 52.33 (C9), 42.30 (C8), 42.29 (C8), 37.7 (C11), 32.1 (C3), 27.5 (C14), 22.7 (C11), 22.3 (C11), 18.4 (C13), 6.7 (C19), 4.4 (C18), 0.1 (C17).



Keto-3.228

2-Methyl-3-(5-(2-oxo-3-(triethylsilyloxy)propyl)furan-2-yl)-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentanone (AJS-V-251). Further structural confirmation of **3.228** was made via derivatization to **Keto-3.228**. A solution of **3.228** (24 mg, 0.05 mmol) in CH_2Cl_2 (0.4 mL) was added to a solution of pyridine (49 mg, 51 μL) and chromium trioxide (31 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) at rt. The reaction mixture was stirred at rt for 1 h. The organic layers were washed with saturated aqueous $CuSO_4$, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was filtered through a short plug of neutrala alumin to yield **keto-3.228** as a colorless oil: ^{1}H NMR (500 MHz) δ 6.14 (d, J = 3.1 Hz, 1 H), 6.09 (dd, J = 3.1, 0.6 Hz, 1 H), 4.25 (s, 2 H), 3.83 (d, 2 H), 3.73 (dd, J = 11.3, 6.2 Hz, 1 H), 2.59 (d, J = 16.8 Hz, 1 H), 2.55–2.50 (m, 1 H), 2.38 (d, J = 16.8 Hz, 1 H), 2.31–2.06 (comp, 3 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.72 (s, 3 H), 0.65 (q, J = 7.9 Hz, 6 H), 0.13 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.4, 205.5, 154.3, 146.9, 108.8, 107.6, 103.5, 87.3, 68.6, 52.3, 42.2, 38.2, 37.7, 27.5, 22.7, 18.4, 6.7, 4.3, 0.1; IR (CH_2Cl_2) 2957, 2877, 2359, 2340, 2174, 1743, 1248, 1098, 1016, 843, 786, 744, 668 cm^{-1}; mass spectrum (CI) m/z 461.2536 [$C_{25}H_{41}O_4Si_2$ (M+1) requires 461.2543], 461 (base), 431.

NMR ASSIGNMENTS: ^{1}H NMR (500 MHz) δ 6.14 (d, J = 3.1 Hz, 1 H, C5-H), 6.09 (dd, J = 3.1, 0.6 Hz, 1 H, C6-H), 4.25 (s, 2 H, C1-H), 3.83 (d, 2 H, C3-H), 3.73 (dd, J = 11.3, 6.2 Hz, 1 H, C8-H), 2.59 (d, J = 16.8 Hz, 1 H, C14-H), 2.55–2.50 (m, 1 H, C10-H), 2.38 (d, J = 16.8 Hz, 1 H, C14-H), 2.31–2.06 (comp, 3 H, C10-H & C9-H), 0.97 (t, J = 7.9 Hz, 9 H, C9-H), 0.72 (s, 3 H, C13-H), 0.65 (q, J = 7.9 Hz, 6 H, C18-H), 0.13 (s, 9 H, C17-H); ^{13}C NMR (125 MHz) δ 219.4, 205.5, 154.3, 146.9, 108.8, 107.6, 103.5, 87.3, 68.6, 52.3, 42.2, 38.2, 37.7, 27.5, 22.7, 18.4, 6.7, 4.3, 0.1.



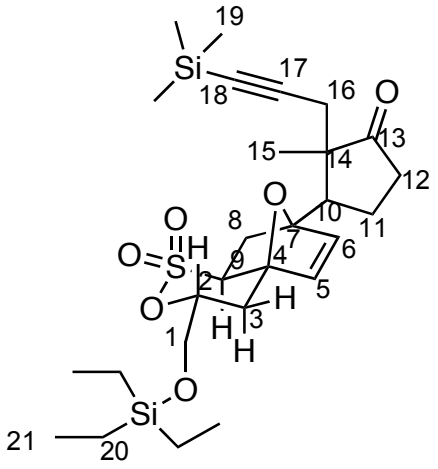
3.224

1-(5-(2-Methyl-3-oxo-2-(3-(trimethylsilyl)prop-2-ynyl)cyclopentyl)furan-2-yl)-3-(triethylsilyloxy)propan-2-yl ethenesulfonate (3.224) (AJS-V-250). Vinylsulfonylchloride (20 mg, 0.16 mmol) was added to a solution of **3.228** (75 mg, 0.16 mmol) and triethylamine (33 mg, 0.32 mmol, 45 μL) in THF (0.7 mL) at 0 ˚C. The reaction mixture was stirred at 0 ˚C for 2 h and then at room temperature for 12 h. The reaction was poured onto ice and the mixture was extracted with Et_2O (3 x 3 mL). The combined organic layers were washed with brine (5 mL), aqueous 1 N HCl (1 mL), and saturated aqueous

$NaHCO_3$ (2 mL). The layers were dried ($MgSO_4$) and the solvent was removed under reduce pressure. The residue was purified by flash chromatography, eluting with pentane/Et_2O (4:1) to yield 88 mg (100%) of **3.224** as a colorless oil: ^1H NMR (500 MHz) δ 6.42 (dd, J = 16.7, 9.8 Hz, 0.5 H), 6.35 (dd, J = 16.6, 9.2 Hz), 6.30 (d, J = 16.7 Hz, 0.5 H), 6.28 (d, J = 16.6 Hz, 0.5 H), 6.07 (m, 1 H), 6.04 (m, 1 H), 5.96 (d, J = 9.8 Hz, 0.5 H), 5.93 (d, J = 9.2 Hz, 0.5 H), 4.69–4.62 (m, 1 H), 3.74–3.67 (comp, 3 H), 3.06 (dd, J = 15.4, 5.7 Hz, 1 H), 2.99 (dd, J = 15.4, 6.8 Hz, 0.5 H), 2.98 (dd, J = 15.4, 6.7 Hz, 0.5 H), 2.58 (d, J = 16.9 Hz, 0.5 H), 2.57 (d, J = 16.8 Hz, 0.5 H), 2.36 (d, J = 16.9 Hz, 0.5 H), 2.35 (d, J = 16.8 Hz, 0.5 H), 2.55–2.41 (m, 1 H), 2.32–2.03 (comp, 3 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.69 (s, 3 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.11 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.3, 219.2, 154.0, 153.9, 149.1, 149.1, 133.5, 133.3, 128.6, 128.5, 108.7, 107.6, 107.5, 103.4, 103.1, 88.1, 88.0, 87.4, 87.3, 81.7, 63.7, 63.6, 52.3, 42.3, 42.2, 37.6, 30.4, 30.3, 27.5, 27.4, 22.7, 18.4, 18.3, 6.4, 4.3, 4.2, 0.08, 0.06; IR (CH_2Cl_2) 2958, 2877, 2175, 1744, 1641, 1367, 1249, 1173, 921, 845, 747 cm^{-1}; mass spectrum (CI) m/z 553.2465 [$C_{27}H_{45}O_6Si_2S$ (M+1) requires 553.2475], 553 (base), 554.

NMR Assignments: ^1H NMR (500 MHz) δ 6.42 (dd, J = 16.7, 9.8 Hz, 0.5 H, C20-H), 6.35 (dd, J = 16.6, 9.2 Hz, C20-H), 6.30 (d, J = 16.7 Hz, 0.5 H, C21-H), 6.28 (d, J = 16.6 Hz, 0.5 H, C21-H), 6.07 (m, 1 H, C5-H), 6.04 (m, 1 H, C6-H), 5.96 (d, J = 9.8 Hz, 0.5 H, C21-H), 5.93 (d, J = 9.2 Hz, 0.5 H, C21-H), 4.69–4.62 (m, 1 H, C2-H), 3.74–3.67 (comp, 3 H, C1-H & C8-H), 3.06 (dd, J = 15.4, 5.7 Hz, 1 H, C3-H), 2.99 (dd, J = 15.4, 6.8 Hz, 0.5 H, C3-H), 2.98 (dd, J = 15.4, 6.7 Hz, 0.5 H, C3-H), 2.58 (d, J = 16.9 Hz, 0.5 H, C14-H), 2.57 (d, J = 16.8 Hz,

0.5 H, C14-H), 2.36 (d, *J* = 16.9 Hz, 0.5 H, C14-H), 2.35 (d, *J* = 16.8 Hz, 0.5 H, C14-H), 2.55–2.41 (m, 1 H, C10-H), 2.32–2.03 (comp, 3 H, C10-H & C9-H), 0.94 (t, *J* = 7.9 Hz, 9 H, C19-H), 0.69 (s, 3 H, C13-H), 0.60 (q, *J* = 7.9 Hz, 6 H, C18-H), 0.11 (s, 9 H, C17-H); ^{13}C NMR (125 MHz) δ 219.3 (C11), 219.2 (C11), 154.0 (C4), 153.9 (C4), 149.1 (C7), 149.0 (C7), 133.5 (C20), 133.3 (C20), 128.6 (C21), 128.5 (C21), 108.7 (C5), 107.6 (C6), 107.5 (C6), 103.4 (C16), 103.1 (C16), 88.1 (C15), 88.0 (C15), 81.7 (C2), 63.7 (C1), 63.6 (C1), 52.3 (C12), 42.3 (C8), 42.2 (C8), 37.6 (C14), 30.4 (C3), 30.3 (C3), 27.5 (C10), 27.4 (C10), 22.7 (C9), 18.4 (C13), 18.3 (C13), 6.4 (C19), 4.3 (C18), 4.2 (C18), 0.08 (C17), 0.06 (C17).



3.223

Diels-Alder Cycloaddition to Furnish Cycloadduct 3.223. A solution of **3.224** (15 mg, 0.03 mmol) in benzene (0.3 mL) was heated at 75 ˚C for 12 h. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was purified via flash chromatography, eluting with pentane/Et_2O (3:1) to give two diastereomers (1:1 ratio). **3.223 (first**

diastereomer): ^{1}H NMR (500 MHz) δ 6.85 (d, J = 5.6 Hz, 1 H), 6.09 (d, J = 5.6 Hz, 1 H), 4.87 (dtd, 12.3, 4.1, 2.1 Hz, 1 H), 3.92 (dd, J = 11.6, 4.1 Hz, 1 H), 3.85 (dd, J = 11.6, 4.1 Hz, 1 H), 3.18–3.12 (comp, 2 H), 2.75 (d, J = 17.2 Hz, 1 H), 2.60 (dd, J = 12.3, 3.2 Hz, 1 H), 2.54–2.47 (comp, 2 H), 2.28 (d, J = 17.2 Hz, 1 H), 2.27–2.02 (comp, 4 H), 1.82 (dd, J = 12.1, 7.9 Hz, 1 H), 0.98 (t, J = 7.8 Hz, 9 H), 0.96 (s, 3 H),0.65 (q, J = 7.8 Hz, 6 H), 0.13 (s, 9 H); ^{13}C NMR (125 MHz) δ 219.6, 141.3, 135.8, 103.1, 90.6, 88.8, 87.8, 80.5, 63.9, 58.6, 51.8, 43.4, 36.6, 32.8, 29.3, 28.3, 20.4, 19.7, 6.7, 4.3, 0.1; IR (CH_2Cl_2) 2957, 2876, 2174, 1742, 1366, 1249, 1173, 1140, 912, 845, 746 cm^{-1}; mass spectrum (CI) m/z 553.2484 [$C_{27}H_{45}O_6Si_2S$ (M+1) requires 553.2475], 553 (base), 554, 523.

NMR Assignments FOR 3.223 (first diastereomer): ^{1}H NMR (500 MHz) δ 6.85 (d, J = 5.6 Hz, 1 H, C5-H), 6.09 (d, J = 5.6 Hz, 1 H, C6-H), 4.87 (dtd, 12.3, 4.1, 2.1 Hz, 1 H, C2-H), 3.92 (dd, J = 11.6, 4.1 Hz, 1 H, C1-H), 3.85 (dd, J = 11.6, 4.1 Hz, 1 H, C1-H), 3.18–3.12 (comp, 2 H, C9-H & C10-H), 2.75 (d, J = 17.2 Hz, 1 H, C16-H), 2.60 (dd, J = 12.3, 3.2 Hz, 1 H, C8-H), 2.54–2.47 (comp, 2 H, C3-H & C12-H), 2.28 (d, J = 17.2 Hz, 1 H, C16-H), 2.27–2.02 (comp, 4 H, C11-H & C3-H), 1.82 (dd, J = 12.3, 7.9 Hz, 1 H, C8-H), 0.98 (t, J = 7.8 Hz, 9 H, C21-H), 0.96 (s, 3 H, C15-H), 0.65 (q, J = 7.8 Hz, 6 H, C20-H), 0.13 (s, 9 H, C19-H); ^{13}C NMR (125 MHz) δ 219.6 (C13), 141.3 (C5), 135.8 (C6), 103.1 (C18), 90.6 (C17), 88.8 (C4), 87.8 (C7), 80.5 (C2), 63.9 (C1), 58.6 (C9), 51.8 (C14), 43.4 (C10), 36.6 (C12), 32.8 (C8), 29.3 (C3), 28.3 (C16), 20.4 (C11), 19.7 (C15), 6.7 (C21), 4.3 (C20), 0.1 (C19).

3.223 (second diastereomer): ^{1}H NMR (500 MHz) δ 6.54 (d, J = 5.6 Hz, 1 H), 6.06 (d, J = 5.6 Hz, 1 H), 4.86 (dtd, J = 12.1, 4.0, 2.0 Hz), 3.90 (dd, J = 11.6, 4.0 Hz, 1 H), 3.85 (dd, J = 11.6, 4.0 Hz, 1 H), 3.19 (dd, J = 7.9, 3.3 Hz, 1 H), 3.14 (dd, J = 12.6, 6.0 Hz, 1 H), 2.68 (d, J = 17.0 Hz, 1 H), 2.54–2.43 (comp, 3 H), 2.50 (d, J = 17.0 Hz, 1 H), 2.31 (dd, J = 15.3, 2.0 Hz, 1 H), 2.24–2.14 (comp, 2 H), 1.97 (dd, J = 12.1, 7.9 Hz, 1 H), 1.94–1.89 (m, 1 H), 1.02 (s, 3 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.65 (q, J = 8.0 Hz, 6 H), 0.13 (s, 9H); ^{13}C NMR (125 MHz) δ 219.6, 141.9, 134.7, 103.5, 91.2, 88.1, 88.0, 80.4, 63.9, 58.9, 51.8, 44.4, 37.2, 33.7, 29.3, 28.6, 21.9, 18.8, 6.7, 4.3, 0.09; IR (CH_2Cl_2) 2957, 2876, 1742, 1365, 1249, 1172, 1138, 1039, 898, 845, 746 cm^{-1}; mass spectrum (CI) m/z 553.2469 [$C_{27}H_{45}O_6Si_2S$ (M+1) requires 553.2475], 553 (base), 554, 523.

NMR Assignments: 3.223 (second diastereomer): ^{1}H NMR (500 MHz) δ 6.54 (d, J = 5.6 Hz, 1 H, C5-H), 6.06 (d, J = 5.6 Hz, 1 H, C6-H), 4.86 (dtd, J = 12.1, 4.0, 2.0 Hz, C2-H), 3.90 (dd, J = 11.6, 4.0 Hz, 1 H, C1-H), 3.85 (dd, J = 11.6, 4.0 Hz, 1 H, C1-H), 3.19 (dd, J = 7.9, 3.3 Hz, 1 H, C9-H), 3.14 (dd, J = 12.6, 6.0 Hz, 1 H, C10-H), 2.68 (d, J = 17.0 Hz, 1 H, C16-H), 2.54–2.43 (comp, 3 H, C8-H, C3-H, & C12-H), 2.50 (d, J = 17.0 Hz, 1 H, C16-H), 2.31 (dd, J = 15.3, 2.0 Hz, 1 H, C3-H), 2.24–2.14 (comp, 2 H, C12-H & C11-H), 1.97 (dd, J = 12.1, 7.9 Hz, 1 H, C8-H), 1.94–1.89 (m, 1 H, C11-H), 1.02 (s, 3 H, C14-H), 0.98 (t, J = 8.0 Hz, 9 H, C21-H), 0.65 (q, J = 8.0 Hz, 6 H, C20-H), 0.13 (s, 9H, C19-H); ^{13}C NMR (125 MHz) δ 219.6 (C13), 141.9 (C5), 134.7 (C6), 103.5 (C18), 91.2 (C17), 88.1 (C4), 88.0 (C7), 80.4 (C2), 63.9 (C1), 58.9 (C9), 51.8 (C14), 44.4

(C10), 37.2 (12), 33.7 (C8), 29.3 (C3), 28.6 (C16), 21.9 (C11), 18.8 (C15), 6.7 (C21), 4.3 (C20), 0.09 (C19).

CRYSTAL STRUCTURE DATA

Crystal Data for 2.126:

Table 1. Crystallographic Data for **2.126**.

Table 2. Fractional coordinates and equivalent isotropic thermal parameters ($Å^2$) for the non-hydrogen atoms of **2.126**.

Table 3. Bond Lengths (Å) and Angles (^{o}) for the non-hydrogen atoms of **2.126**.

Table 4. Anisotropic thermal parameters for the non-hydrogen atoms of **2.126**.

Table 5. Fractional coordinates and isotropic thermal parameters ($Å^2$) for the hydrogen atoms of **2.126**.

Table 6. Torsion Angles (^{o}) for the non-hydrogen atoms of **2.126**.

Table 1. Crystal data and structure refinement for 1.

Empirical formula	C13 H12 O2	
Formula weight	200.23	
Temperature	100(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 6.5551(5) Å	α= 90°.
	b = 7.0695(8) Å	β= 99.376(4)°.
	c = 11.0981(10) Å	γ = 90°.
Volume	507.43(8) $Å^3$	
Z	2	
Density (calculated)	1.310 Mg/m^3	
Absorption coefficient	0.703 mm^{-1}	
F(000)	212	

Crystal size	0.28 x 0.22 x 0.03 mm
Theta range for data collection	6.85 to 69.83°.
Index ranges	-7<=h<=7, -6<=k<=8, -13<=l<=13
Reflections collected	6565
Independent reflections	1662 [R(int) = 0.0726]
Completeness to theta = 69.83°	94.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.70
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1662 / 1 / 137
Goodness-of-fit on F^2	1.108
Final R indices [I>2sigma(I)]	R1 = 0.0591, wR2 = 0.1209
R indices (all data)	R1 = 0.0735, wR2 = 0.1425
Absolute structure parameter	0.1(5)
Largest diff. peak and hole	0.216 and -0.218 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	3045(3)	7853(4)	1814(2)	41(1)
O2	10972(4)	9707(5)	5098(2)	52(1)
C1	5040(5)	8574(6)	1940(3)	37(1)
C2	5512(5)	9174(6)	874(3)	39(1)
C3	3729(5)	8832(6)	-33(3)	35(1)
C4	3212(6)	9099(6)	-1301(3)	42(1)
C5	1275(6)	8571(7)	-1870(3)	47(1)
C6	-173(6)	7766(7)	-1215(3)	45(1)

C7	310(6)	7508(7)	29(4)	41(1)
C8	2250(5)	8032(6)	579(3)	37(1)
C9	6202(5)	8515(7)	3214(3)	39(1)
C10	8516(5)	8833(7)	3310(3)	40(1)
C11	9202(6)	9541(7)	4599(3)	45(1)
C12	7307(5)	10015(8)	5152(3)	44(1)
C13	5545(5)	10045(8)	4055(3)	50(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O1-C1	1.389(4)
O1-C8	1.391(4)
O2-C11	1.208(4)
C1-C2	1.340(5)
C1-C9	1.493(4)
C2-C3	1.433(4)
C2-H2	0.9500
C3-C8	1.391(5)
C3-C4	1.405(5)
C4-C5	1.375(5)
C4-H4	0.9500
C5-C6	1.407(6)
C5-H5	0.9500
C6-C7	1.378(5)
C6-H6	0.9500
C7-C8	1.369(5)
C7-H7	0.9500
C9-C10	1.520(4)
C9-C13	1.536(6)
C9-H9	1.0000
C10-C11	1.513(5)
C10-H10A	0.9900
C10-H10B	0.9900

C11-C12	1.510(5)
C12-C13	1.536(5)
C12-H12A	0.9900
C12-H12B	0.9900
C13-H13A	0.9900
C13-H13B	0.9900
C1-O1-C8	105.1(3)
C2-C1-O1	112.1(3)
C2-C1-C9	133.6(3)
O1-C1-C9	114.3(3)
C1-C2-C3	106.7(3)
C1-C2-H2	126.7
C3-C2-H2	126.7
C8-C3-C4	118.0(3)
C8-C3-C2	106.2(3)
C4-C3-C2	135.7(3)
C5-C4-C3	118.5(3)
C5-C4-H4	120.7
C3-C4-H4	120.7
C4-C5-C6	121.5(3)
C4-C5-H5	119.2
C6-C5-H5	119.2
C7-C6-C5	120.5(4)
C7-C6-H6	119.8
C5-C6-H6	119.8
C8-C7-C6	117.1(4)
C8-C7-H7	121.4
C6-C7-H7	121.4
C7-C8-C3	124.3(3)
C7-C8-O1	125.9(3)
C3-C8-O1	109.8(3)

C1-C9-C10	114.3(3)
C1-C9-C13	113.9(3)
C10-C9-C13	103.2(3)
C1-C9-H9	108.4
C10-C9-H9	108.4
C13-C9-H9	108.4
C11-C10-C9	104.7(3)
C11-C10-H10A	110.8
C9-C10-H10A	110.8
C11-C10-H10B	110.8
C9-C10-H10B	110.8
H10A-C10-H10B	108.9
O2-C11-C12	125.8(4)
O2-C11-C10	125.6(3)
C12-C11-C10	108.7(3)
C11-C12-C13	104.1(3)
C11-C12-H12A	110.9
C13-C12-H12A	110.9
C11-C12-H12B	110.9
C13-C12-H12B	110.9
H12A-C12-H12B	109.0
C12-C13-C9	102.9(3)
C12-C13-H13A	111.2
C9-C13-H13A	111.2
C12-C13-H13B	111.2
C9-C13-H13B	111.2
H13A-C13-H13B	109.1

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}

O1	33(1)	48(2)	44(1)	2(1)	10(1)	0(1)
O2	39(2)	64(3)	53(2)	-6(2)	11(1)	-5(2)
C1	34(2)	24(3)	53(2)	-5(2)	12(2)	-3(2)
C2	34(2)	32(3)	52(2)	0(2)	13(2)	2(2)
C3	40(2)	23(3)	44(2)	1(2)	11(1)	5(2)
C4	50(2)	29(3)	48(2)	3(2)	14(2)	1(2)
C5	53(2)	43(3)	44(2)	-1(2)	6(2)	5(2)
C6	44(2)	33(3)	56(2)	-4(2)	2(2)	9(2)
C7	37(2)	35(3)	52(2)	-1(2)	12(2)	1(2)
C8	39(2)	29(3)	43(2)	-3(2)	9(2)	5(2)
C9	37(2)	37(3)	43(2)	3(2)	11(1)	-3(2)
C10	41(2)	37(3)	45(2)	1(2)	15(2)	2(2)
C11	38(2)	50(3)	48(2)	-1(2)	10(2)	-1(2)
C12	37(2)	52(4)	47(2)	-8(2)	15(2)	-1(2)
C13	39(2)	63(4)	50(2)	-9(2)	19(2)	-2(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

	x	y	z	U(eq)
H2	6783	9719	744	47
H4	4180	9633	-1754	50
H5	906	8755	-2726	57
H6	-1494	7397	-1634	54
H7	-661	6988	486	49
H9	5977	7248	3571	46
H10A	9231	7639	3169	48

H10B	8810	9784	2706	48
H12A	7457	11263	5561	53
H12B	7056	9042	5753	53
H13A	5434	11297	3651	59
H13B	4204	9727	4306	59

Table 6. Torsion angles [°] for 1.

C8-O1-C1-C2	-0.1(4)
C8-O1-C1-C9	-179.8(3)
O1-C1-C2-C3	-0.2(5)
C9-C1-C2-C3	179.4(4)
C1-C2-C3-C8	0.4(5)
C1-C2-C3-C4	-179.1(5)
C8-C3-C4-C5	0.4(6)
C2-C3-C4-C5	179.8(5)
C3-C4-C5-C6	-0.5(6)
C4-C5-C6-C7	0.9(7)
C5-C6-C7-C8	-1.2(7)
C6-C7-C8-C3	1.2(7)
C6-C7-C8-O1	-178.7(4)
C4-C3-C8-C7	-0.8(6)
C2-C3-C8-C7	179.6(4)
C4-C3-C8-O1	179.1(4)
C2-C3-C8-O1	-0.5(5)
C1-O1-C8-C7	-179.7(4)
C1-O1-C8-C3	0.4(4)
C2-C1-C9-C10	-14.1(7)
O1-C1-C9-C10	165.5(4)
C2-C1-C9-C13	104.3(5)
O1-C1-C9-C13	-76.1(4)
C1-C9-C10-C11	156.5(4)

C13-C9-C10-C11	32.2(4)
C9-C10-C11-O2	168.9(5)
C9-C10-C11-C12	-11.5(5)
O2-C11-C12-C13	165.8(5)
C10-C11-C12-C13	-13.9(5)
C11-C12-C13-C9	33.5(5)
C1-C9-C13-C12	-165.4(3)
C10-C9-C13-C12	-40.9(4)

Crystal Data for Exo Diels-Alder Adduct (3.214):

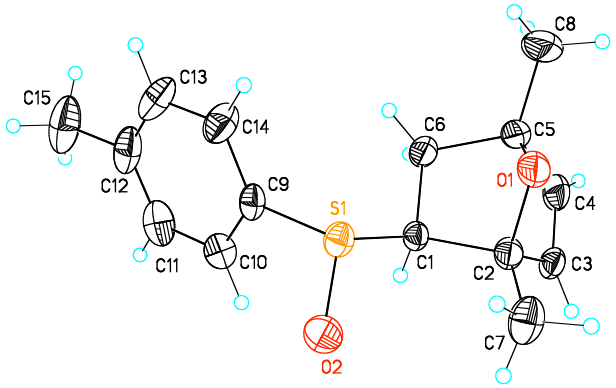


Table 1. Crystal data and structure refinement for 1.

Empirical formula	C15 H18.50 O2.25 S	
Formula weight	266.86	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.6100(4) Å	α= 90°.
	b = 9.1107(6) Å	β= 90°.
	c = 27.1378(14) Å	γ = 90°.

Volume	1387.04(15) $Å^3$
Z	4
Density (calculated)	1.278 Mg/m^3
Absorption coefficient	0.228 mm^{-1}
F(000)	570
Crystal size	0.30 x 0.07 x 0.04 mm
Theta range for data collection	2.69 to 30.00°.
Index ranges	-7<=h<=6, -12<=k<=12, -25<=l<=38
Reflections collected	9792
Independent reflections	3672 [R(int) = 0.0532]
Completeness to theta = 30.00°	98.4 %
Absorption correction	Analytical
Max. and min. transmission	0.992 and 0.933
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3672 / 108 / 171
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0684, wR2 = 0.1315
R indices (all data)	R1 = 0.1107, wR2 = 0.1522
Absolute structure parameter	0.11(13)
Largest diff. peak and hole	0.496 and -0.336 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S1	6994(2)	2944(1)	1271(1)	28(1)

O1	7235(5)	6012(3)	649(1)	41(1)
O2	7477(5)	1517(3)	1017(1)	40(1)
C1	5029(6)	3959(3)	856(1)	22(1)
C2	6486(6)	4672(4)	417(1)	28(1)
C3	4573(6)	5209(4)	67(1)	27(1)
C4	3594(7)	6370(4)	273(1)	38(1)
C5	4877(9)	6562(4)	761(1)	44(1)
C6	3932(8)	5318(4)	1105(1)	35(1)
C7	8524(6)	3826(5)	201(1)	39(1)
C8	4989(13)	8091(4)	977(2)	78(2)
C9	4839(6)	2577(3)	1749(1)	28(1)
C10	3042(7)	1569(4)	1673(1)	37(1)
C11	1458(7)	1273(5)	2053(2)	45(1)
C12	1644(7)	1962(5)	2501(1)	45(1)
C13	3439(8)	2980(5)	2568(1)	49(1)
C14	5064(7)	3291(4)	2193(1)	40(1)
C15	-82(9)	1615(6)	2908(2)	64(1)
O1W	9620(30)	8636(17)	1175(5)	76(4)

Table 3. Bond lengths [Å] and angles [°] for 1.

S1-O2	1.497(2)
S1-C9	1.804(3)
S1-C1	1.826(3)
O1-C2	1.435(4)
O1-C5	1.447(6)
C1-C6	1.538(4)
C1-C2	1.584(4)
C1-H1	1.00
C2-C7	1.498(5)
C2-C3	1.515(5)
C3-C4	1.316(5)
C3-H3	0.95

C4-C5	1.517(5)
C4-H4	0.95
C5-C8	1.514(5)
C5-C6	1.561(5)
C6-H6A	0.99
C6-H6B	0.99
C7-H7A	0.98
C7-H7B	0.98
C7-H7C	0.98
C8-H8A	0.98
C8-H8B	0.98
C8-H8C	0.98
C9-C14	1.375(5)
C9-C10	1.379(5)
C10-C11	1.387(5)
C10-H10	0.95
C11-C12	1.372(6)
C11-H11	0.95
C12-C13	1.382(6)
C12-C15	1.504(5)
C13-C14	1.396(5)
C13-H13	0.95
C14-H14	0.95
C15-H15A	0.98
C15-H15B	0.98
C15-H15C	0.98
O2-S1-C9	106.97(15)
O2-S1-C1	105.41(14)
C9-S1-C1	97.59(15)
C2-O1-C5	96.8(3)
C6-C1-C2	101.9(2)

C6-C1-S1	112.3(2)
C2-C1-S1	111.0(2)
C6-C1-H1	110.5
C2-C1-H1	110.5
S1-C1-H1	110.5
O1-C2-C7	112.7(3)
O1-C2-C3	102.0(3)
C7-C2-C3	117.4(3)
O1-C2-C1	99.8(2)
C7-C2-C1	118.5(3)
C3-C2-C1	103.8(3)
C4-C3-C2	106.7(3)
C4-C3-H3	126.6
C2-C3-H3	126.6
C3-C4-C5	105.4(3)
C3-C4-H4	127.3
C5-C4-H4	127.3
O1-C5-C8	111.2(4)
O1-C5-C4	102.2(3)
C8-C5-C4	117.7(3)
O1-C5-C6	100.6(3)
C8-C5-C6	116.8(3)
C4-C5-C6	106.1(3)
C1-C6-C5	100.8(3)
C1-C6-H6A	111.6
C5-C6-H6A	111.6
C1-C6-H6B	111.6
C5-C6-H6B	111.6
H6A-C6-H6B	109.4
C2-C7-H7A	109.5
C2-C7-H7B	109.5

H7A-C7-H7B	109.5
C2-C7-H7C	109.5
H7A-C7-H7C	109.5
H7B-C7-H7C	109.5
C5-C8-H8A	109.5
C5-C8-H8B	109.5
H8A-C8-H8B	109.5
C5-C8-H8C	109.5
H8A-C8-H8C	109.5
H8B-C8-H8C	109.5
C14-C9-C10	120.8(3)
C14-C9-S1	118.8(3)
C10-C9-S1	120.4(3)
C9-C10-C11	119.2(3)
C9-C10-H10	120.4
C11-C10-H10	120.4
C12-C11-C10	121.3(4)
C12-C11-H11	119.3
C10-C11-H11	119.3
C11-C12-C13	118.7(4)
C11-C12-C15	120.4(4)
C13-C12-C15	120.9(4)
C12-C13-C14	121.0(4)
C12-C13-H13	119.5
C14-C13-H13	119.5
C9-C14-C13	118.9(4)
C9-C14-H14	120.5
C13-C14-H14	120.5
C12-C15-H15A	109.5
C12-C15-H15B	109.5
H15A-C15-H15B	109.5

C12-C15-H15C	109.5
H15A-C15-H15C	109.5
H15B-C15-H15C	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	28(1)	30(1)	24(1)	4(1)	-2(1)	2(1)
O1	58(2)	36(1)	28(1)	1(1)	-6(1)	-20(1)
O2	46(2)	34(1)	40(1)	2(1)	4(1)	16(1)
C1	23(2)	22(2)	20(1)	3(1)	-1(1)	1(1)
C2	33(2)	28(2)	22(2)	1(1)	-3(1)	-9(2)
C3	32(2)	30(2)	17(2)	3(1)	-1(1)	-3(2)
C4	57(3)	30(2)	28(2)	12(2)	4(2)	8(2)
C5	88(3)	22(2)	23(2)	1(1)	2(2)	-1(2)
C6	56(2)	26(2)	23(2)	3(1)	7(2)	9(2)
C7	26(2)	54(2)	38(2)	11(2)	5(2)	3(2)
C8	166(5)	25(2)	41(2)	-5(2)	0(3)	0(3)
C9	29(2)	29(2)	24(2)	9(1)	-1(1)	3(1)
C10	44(2)	32(2)	35(2)	3(2)	1(2)	0(2)
C11	38(2)	44(2)	51(2)	17(2)	0(2)	-4(2)
C12	44(2)	56(2)	35(2)	21(2)	2(2)	11(2)
C13	55(3)	71(3)	21(2)	2(2)	-1(2)	5(3)
C14	41(2)	52(2)	26(2)	3(2)	-4(2)	-5(2)
C15	53(3)	90(4)	48(2)	33(2)	16(2)	19(3)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^{\ 3}$) for 1.

	x	y	z	U(eq)

H1	3748	3302	726	26
H3	4160	4789	-242	32
H4	2348	6961	144	46
H6A	4513	5438	1447	42
H6B	2169	5275	1105	42
H7A	9244	4395	-67	59
H7B	7940	2888	72	59
H7C	9721	3643	457	59
H8A	5982	8080	1275	116
H8B	3377	8418	1063	116
H8C	5681	8766	735	116
H10	2891	1083	1365	44
H11	220	578	2002	54
H13	3570	3477	2875	59
H14	6305	3984	2243	48
H15A	689	970	3150	95
H15B	-1484	1121	2771	95
H15C	-575	2527	3070	95

Table 6. Torsion angles [°] for 1.

O2-S1-C1-C6	168.1(2)
C9-S1-C1-C6	58.1(3)
O2-S1-C1-C2	-78.5(2)
C9-S1-C1-C2	171.5(2)
C5-O1-C2-C7	174.6(3)
C5-O1-C2-C3	47.8(3)
C5-O1-C2-C1	-58.7(3)
C6-C1-C2-O1	34.5(3)

S1-C1-C2-O1	-85.2(3)
C6-C1-C2-C7	157.2(3)
S1-C1-C2-C7	37.4(3)
C6-C1-C2-C3	-70.5(3)
S1-C1-C2-C3	169.7(2)
O1-C2-C3-C4	-30.6(3)
C7-C2-C3-C4	-154.2(3)
C1-C2-C3-C4	72.8(3)
C2-C3-C4-C5	-0.6(4)
C2-O1-C5-C8	-174.9(3)
C2-O1-C5-C4	-48.5(3)
C2-O1-C5-C6	60.7(3)
C3-C4-C5-O1	31.4(4)
C3-C4-C5-C8	153.5(4)
C3-C4-C5-C6	-73.6(4)
C2-C1-C6-C5	1.5(3)
S1-C1-C6-C5	120.4(3)
O1-C5-C6-C1	-37.0(3)
C8-C5-C6-C1	-157.5(4)
C4-C5-C6-C1	69.1(4)
O2-S1-C9-C14	141.6(3)
C1-S1-C9-C14	-109.6(3)
O2-S1-C9-C10	-36.6(3)
C1-S1-C9-C10	72.1(3)
C14-C9-C10-C11	-0.3(5)
S1-C9-C10-C11	177.9(3)
C9-C10-C11-C12	0.0(6)
C10-C11-C12-C13	0.6(6)
C10-C11-C12-C15	-179.5(4)
C11-C12-C13-C14	-1.0(6)
C15-C12-C13-C14	179.1(4)

C10-C9-C14-C13	0.0(6)
S1-C9-C14-C13	-178.3(3)
C12-C13-C14-C9	0.7(6)

Crystal Data for Endo Diels-Alder Adduct:

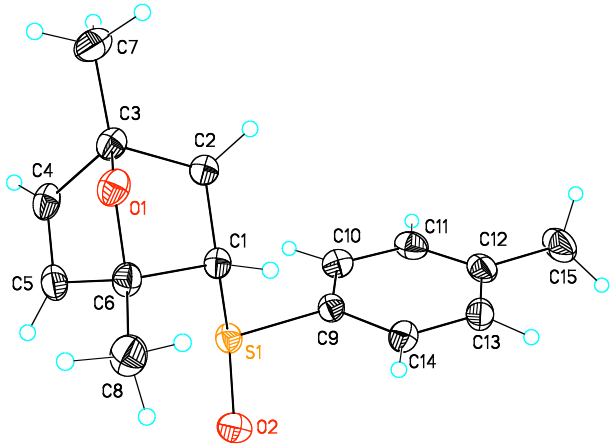


Table 1. Crystal data and structure refinement for 1.

Empirical formula	C15 H18 O2 S	
Formula weight	262.35	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Orhtorhombic	
Space group	P212121	
Unit cell dimensions	a = 7.04400(1) Å	α= 90°.
	b = 12.5470(2) Å	β= 90°.
	c = 15.3720(2) Å	γ = 90°.
Volume	1358.59(3) $Å^3$	
Z	4	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.230 mm^{-1}	
F(000)	560	
Crystal size	0.25 x 0.20 x 0.15 mm	

Theta range for data collection	2.10 to 32.50°.
Index ranges	-10<=h<=10, -18<=k<=18, -23<=l<=23
Reflections collected	4901
Independent reflections	4901
Completeness to theta = 32.50°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4901 / 108 / 237
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0300, wR2 = 0.0721
R indices (all data)	R1 = 0.0356, wR2 = 0.0752
Absolute structure parameter	0.00(4)
Extinction coefficient	$1.1(2)x10^{-5}$
Largest diff. peak and hole	0.253 and -0.231 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S1	5952(1)	3300(1)	3335(1)	21(1)
O1	3728(1)	2636(1)	1055(1)	25(1)
C1	5390(1)	2589(1)	2339(1)	20(1)
O2	7634(1)	3998(1)	3139(1)	30(1)
C2	3583(2)	1904(1)	2433(1)	22(1)
C3	2300(1)	2385(1)	1705(1)	23(1)
C4	1735(2)	3494(1)	2016(1)	26(1)
C5	3279(2)	4095(1)	1934(1)	26(1)
C6	4822(1)	3367(1)	1577(1)	23(1)
C7	797(2)	1656(1)	1344(1)	31(1)

C8	6445(2)	3849(1)	1074(1)	32(1)
C9	6809(2)	2177(1)	3938(1)	20(1)
C10	5691(2)	1756(1)	4595(1)	24(1)
C11	6387(2)	914(1)	5095(1)	28(1)
C12	8176(2)	485(1)	4935(1)	28(1)
C13	9285(2)	933(1)	4276(1)	27(1)
C14	8625(2)	1783(1)	3781(1)	24(1)
C15	8890(3)	-457(1)	5447(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

S1-O2	1.5034(9)
S1-C9	1.7914(10)
S1-C1	1.8157(10)
O1-C6	1.4411(13)
O1-C3	1.4523(13)
C1-C2	1.5430(14)
C1-C6	1.5763(14)
C1-H1	0.967(13)
C2-C3	1.5599(15)
C2-H2A	0.991(14)
C2-H2B	0.963(15)
C3-C7	1.5047(15)
C3-C4	1.5251(15)
C4-C5	1.3295(16)
C4-H4	0.949(15)
C5-C6	1.5221(15)
C5-H5	0.934(15)
C6-C8	1.5061(15)
C7-H7B	0.949(19)
C7-H7A	0.991(17)
C7-H7C	0.950(19)
C8-H8C	0.963(16)

C8-H8B	1.017(17)
C8-H8A	1.024(18)
C9-C10	1.3859(14)
C9-C14	1.3927(14)
C10-C11	1.3957(16)
C10-H10	0.982(16)
C11-C12	1.3918(18)
C11-H11	0.972(17)
C12-C13	1.3974(18)
C12-C15	1.5064(16)
C13-C14	1.3899(15)
C13-H13	0.970(19)
C14-H14	0.910(16)
C15-H15A	0.94(2)
C15-H15B	1.00(3)
C15-H15C	0.95(2)
O2-S1-C9	107.21(5)
O2-S1-C1	106.79(5)
C9-S1-C1	97.11(5)
C6-O1-C3	97.24(7)
C2-C1-C6	101.83(8)
C2-C1-S1	111.99(7)
C6-C1-S1	112.20(7)
C2-C1-H1	113.7(8)
C6-C1-H1	110.7(8)
S1-C1-H1	106.6(8)
C1-C2-C3	101.26(8)
C1-C2-H2A	111.7(9)
C3-C2-H2A	110.2(8)
C1-C2-H2B	112.9(9)
C3-C2-H2B	114.4(9)

H2A-C2-H2B	106.4(12)
O1-C3-C7	111.48(9)
O1-C3-C4	101.45(8)
C7-C3-C4	119.16(9)
O1-C3-C2	100.14(8)
C7-C3-C2	115.89(9)
C4-C3-C2	106.18(9)
C5-C4-C3	105.89(9)
C5-C4-H4	129.3(9)
C3-C4-H4	124.6(9)
C4-C5-C6	106.17(9)
C4-C5-H5	127.1(10)
C6-C5-H5	126.4(10)
O1-C6-C8	112.07(9)
O1-C6-C5	101.59(8)
C8-C6-C5	119.10(10)
O1-C6-C1	98.94(8)
C8-C6-C1	115.89(8)
C5-C6-C1	106.53(8)
C3-C7-H7B	110.6(11)
C3-C7-H7A	110.6(9)
H7B-C7-H7A	105.5(14)
C3-C7-H7C	111.1(12)
H7B-C7-H7C	108.6(15)
H7A-C7-H7C	110.2(14)
C6-C8-H8C	110.0(10)
C6-C8-H8B	109.2(10)
H8C-C8-H8B	111.0(13)
C6-C8-H8A	110.6(10)
H8C-C8-H8A	110.5(13)
H8B-C8-H8A	105.5(13)

C10-C9-C14	120.86(10)
C10-C9-S1	119.06(8)
C14-C9-S1	119.95(8)
C9-C10-C11	119.34(10)
C9-C10-H10	118.0(10)
C11-C10-H10	122.6(10)
C12-C11-C10	120.93(11)
C12-C11-H11	121.3(11)
C10-C11-H11	117.7(11)
C11-C12-C13	118.57(10)
C11-C12-C15	120.90(12)
C13-C12-C15	120.51(12)
C14-C13-C12	121.26(11)
C14-C13-H13	116.9(10)
C12-C13-H13	121.8(10)
C13-C14-C9	119.00(10)
C13-C14-H14	122.1(10)
C9-C14-H14	118.9(10)
C12-C15-H15A	111.5(12)
C12-C15-H15B	108.4(15)
H15A-C15-H15B	113(2)
C12-C15-H15C	109.9(12)
H15A-C15-H15C	104.5(17)
H15B-C15-H15C	110(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	22(1)	19(1)	21(1)	-1(1)	-1(1)	3(1)
O1	24(1)	30(1)	20(1)	-2(1)	-2(1)	4(1)

C1	20(1)	20(1)	19(1)	0(1)	-1(1)	3(1)
O2	30(1)	25(1)	36(1)	3(1)	-4(1)	-5(1)
C2	21(1)	22(1)	24(1)	1(1)	-1(1)	1(1)
C3	20(1)	26(1)	23(1)	-2(1)	-1(1)	2(1)
C4	22(1)	29(1)	26(1)	-1(1)	-3(1)	9(1)
C5	28(1)	22(1)	27(1)	2(1)	-3(1)	7(1)
C6	22(1)	24(1)	22(1)	3(1)	-1(1)	2(1)
C7	24(1)	37(1)	32(1)	-7(1)	-5(1)	-2(1)
C8	29(1)	37(1)	29(1)	11(1)	3(1)	0(1)
C9	23(1)	20(1)	18(1)	-1(1)	-3(1)	2(1)
C10	25(1)	27(1)	21(1)	-2(1)	1(1)	-1(1)
C11	36(1)	26(1)	23(1)	2(1)	-2(1)	-6(1)
C12	37(1)	20(1)	25(1)	-1(1)	-11(1)	-1(1)
C13	27(1)	25(1)	30(1)	-4(1)	-6(1)	5(1)
C14	23(1)	26(1)	22(1)	-1(1)	-1(1)	2(1)
C15	55(1)	25(1)	40(1)	7(1)	-17(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1.

	x	y	z	U(eq)
H1	6508(19)	2183(10)	2186(8)	17(3)

H2A	3840(20)	1141(11)	2313(9)	25(3)
H2B	3040(20)	1936(12)	3008(10)	32(4)
H4	540(20)	3669(11)	2261(9)	26(4)
H5	3430(20)	4800(12)	2114(10)	27(4)
H7B	-120(30)	1489(15)	1777(12)	50(5)
H7A	1360(20)	964(13)	1169(10)	35(4)
H7C	160(30)	1974(15)	865(12)	49(5)
H8C	5960(20)	4291(13)	612(10)	35(4)
H8B	7280(20)	4277(14)	1487(11)	43(5)
H8A	7310(30)	3264(15)	829(11)	44(5)
H10	4430(20)	2075(13)	4694(10)	33(4)
H11	5620(30)	672(14)	5581(11)	39(4)
H13	10570(30)	696(14)	4165(11)	44(5)
H14	9330(20)	2079(13)	3348(11)	36(4)
H15A	8370(30)	-470(16)	6012(14)	56(6)
H15B	10310(40)	-440(20)	5449(17)	90(8)
H15C	8460(30)	-1103(17)	5186(13)	58(6)

Table 6. Torsion angles [°] for 1.

O2-S1-C1-C2	-175.66(7)
C9-S1-C1-C2	73.91(7)
O2-S1-C1-C6	-61.86(8)
C9-S1-C1-C6	-172.29(7)
C6-C1-C2-C3	0.92(9)
S1-C1-C2-C3	120.98(7)
C6-O1-C3-C7	176.63(9)
C6-O1-C3-C4	48.75(9)
C6-O1-C3-C2	-60.22(8)
C1-C2-C3-O1	34.93(9)
C1-C2-C3-C7	154.94(9)
C1-C2-C3-C4	-70.26(10)
O1-C3-C4-C5	-30.75(11)

C7-C3-C4-C5	-153.50(11)
C2-C3-C4-C5	73.47(11)
C3-C4-C5-C6	-0.36(12)
C3-O1-C6-C8	-177.21(9)
C3-O1-C6-C5	-48.98(9)
C3-O1-C6-C1	60.06(8)
C4-C5-C6-O1	31.65(11)
C4-C5-C6-C8	155.22(10)
C4-C5-C6-C1	-71.43(11)
C2-C1-C6-O1	-36.70(9)
S1-C1-C6-O1	-156.61(7)
C2-C1-C6-C8	-156.64(10)
S1-C1-C6-C8	83.46(10)
C2-C1-C6-C5	68.29(10)
S1-C1-C6-C5	-51.61(10)
O2-S1-C9-C10	143.61(8)
C1-S1-C9-C10	-106.31(9)
O2-S1-C9-C14	-32.34(10)
C1-S1-C9-C14	77.74(9)
C14-C9-C10-C11	-1.07(16)
S1-C9-C10-C11	-176.98(8)
C9-C10-C11-C12	-0.76(16)
C10-C11-C12-C13	1.57(16)
C10-C11-C12-C15	-177.12(11)
C11-C12-C13-C14	-0.60(16)
C15-C12-C13-C14	178.11(11)
C12-C13-C14-C9	-1.17(16)
C10-C9-C14-C13	2.02(15)
S1-C9-C14-C13	177.89(8)

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Vita

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